A Prospective Study on the Prevalence, Extent of Disease and Outcome of Eosinophilic Gastroenteritis in Patients Presenting with Lower Abdominal Symptoms

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Background/Aims: The epidemiology of eosinophilic gastroenteritis remains unclear. We aim to determine the prevalence of eosinophilic gastroenteritis in patients with lower abdominal symptoms. **Methods:** In a prospective study, colonoscopy was performed on 2,469 consecutive patients. Biopsies were taken from the terminal ileum and ascending, transverse, descending and sigmoid colon in all patients. **Results:** Sixty-four of the 2,469 patients (2.6%) had eosinophilic gastroenteritis. Only five of the 64 patients (7.8%) with eosinophilic gastroenteritis had endoscopic mucosal abnormalities during colonoscopy. Six of these 64 patients (9.4%) had severe disease at presentation, and seven of these 64 patients (10.9%) required systemic steroid treatment. An elevated absolute peripheral eosinophil count was independently associated with severe disease at presentation (4/6 [66.7%] vs 3/58 [5.2%], p=0.005; odds ratio [OR], 25.320; 95% confidence interval [CI], 2.628 to 243.910), and severe disease at the time of presentation was independently associated with the use of systemic steroid treatment (6/7 [85.7%] vs 0/57 [0%], p=0.008; OR, 18.021; 95% CI, 2.163 to 150.152). **Conclusions:** The prevalence of eosinophilic gastroenteritis is common, and patients usually present normal-appearing mucosa on colonoscopy. Those with severe disease at presentation usually have a raised absolute peripheral eosinophil count and should be commenced on systemic steroids as an initial therapy. **(Gut Liver 2018;12:288-296)**

Key Words: Eosinophilic enteropathy; Prevalence; Complications; Systemic steroid

INTRODUCTION

Eosinophilic gastroenteritis was first described in the 1930's. It has garnered increasing attention over the past 10 years.[1,2] Its recent incidence is estimated to be 28 per 100,000 per year with studies showing an increasing prevalence over the last 16 years.[3-7]

With the advent of flexible endoscopies, many of the eosinophilic gastroenteritis are diagnosed by mucosa biopsies. This increased use of flexible endoscopies may account for the shift of eosinophilic gastroenteritis towards more mucosal disease type being reported recently.[8-11]

Despite the increased ease of diagnosis, the epidemiology of eosinophilic gastroenteritis remains unclear due to its low prevalence and the lack of prospective studies. Most of the data on eosinophilic gastroenteritis so far have been gathered from retrospective case series or case reports.

Furthermore, the optimal treatment for eosinophilic gastroenteritis is still uncertain and there has been no consensus regarding the treatment of eosinophilic gastroenteritis. This is because of the lack of prospective controlled clinical trials.

Therefore, we have performed a prospective study to determine the prevalence and outcome of eosinophilic gastroenteritis in those who had presented with lower abdominal symptoms.

MATERIALS AND METHODS

1. Patients

Patients with tenesmus, change in bowel habit, per rectal bleeding, abdominal discomfort/pain located in the following abdominal regions: right lumbar, umbilical, left lumbar, right iliac, hypogastrium or left iliac region, mucous in stool, diarrhea or constipation seen at the Centre For Digestive Diseases from

February 2009 to September 2015 were included into this prospective study.

2. Colonoscopy

One experienced endoscopist (C.K.H) performed all the conventional white-light colonoscopy (Olympus, Tokyo, Japan) under conscious sedation with intravenous midazolam and pethidine. All patients had two blind biopsies taken from the terminal ileum, ascending, transverse, descending and sigmoid colon, respectively, for histology.

Pathology proximal to the splenic flexure on withdrawal of the colonoscope was classified as a proximal lesion. In those with endoscopic mucosal abnormality detected on colonoscopy, biopsies were taken from the mucosal abnormality as well as from the normal mucosa. Patients with incomplete examination being defined as failure to cannulate the terminal ileum were excluded from this study.

3. Definition of eosinophilic gastroenteritis

Eosinophilic gastroenteritis was defined as a dense and diffuse eosinophilic infiltrate of the lamina propria of more than 20 eosinophils per high powered field (×400) associated with one or more features such as eosinophilic cryptitis, degranulating eosinophils, eosinophilic microabscesses, or, extension of the eosinophilic infiltrate into the muscularis mucosae or submucosa of the terminal ileum or colon.[1,5,10,12] All biopsy specimens have been interpreted by two experienced histopathologists (Wai Ng and Kai Leung).

4. Further investigation on those diagnosed eosinophilic gastroenteritis

Every patient diagnosed with eosinophilic gastroenteritis had an oesophagogastroduodenoscopy (OGD) (Olympus) under in-travenous midazolam with two blind biopsies each obtained respectively, from the mid-esophagus, lesser curve, greater curve, antrum and second part of duodenum. Diagnosis of eosinophilic esophagitis, eosinophilic gastritis or eosinophilic duodenitis was based on the histological criteria previously defined by Collins.[12]

Complete blood picture, erythrocyte sedimentation rate, liver biochemistry, urea, electrolytes, stool for ova and parasites (three samples), anti-neutrophilic cytoplasmic antibody (ANCA), antinuclear antibody, immunoglobulin E, chest X-ray, serological tests for *Trichinella spiralis*, *Wuchereria bancrofti*, *Toxocara canis*, *Schistosoma* and *Echinococcus* were performed. All biopsy specimens were histologically examined for intestinal spirochetosis by identifying the typical haematoxyphilic fringe on the brush border of the surface epithelium on hematoxylin and eosin staining and confirmed by Warthin-Starry silver staining. Additionally, a computerized tomography of the abdomen and pelvis (plain and contrast) was also performed.

A bone marrow biopsy was performed in those found with an absolute peripheral count $\geq 1.5 \times 10^9$/L. Chromosome 4Q12 deletion together with the presence of tyrosine kinase created by fusion of the FIP1-like gene and platelet-derived growth factor receptor α gene were also checked to rule out the possibility of hypereosinophilic syndrome.[13]

5. Complications or severe disease at the time of presentation

Those found to have biliopancreatic complications, liver involvement such as periportal edema, volvulus, intussusception, intestinal perforation, ascites or protein losing enteropathy would be classified as suffering from complications or severe disease.[1,14]
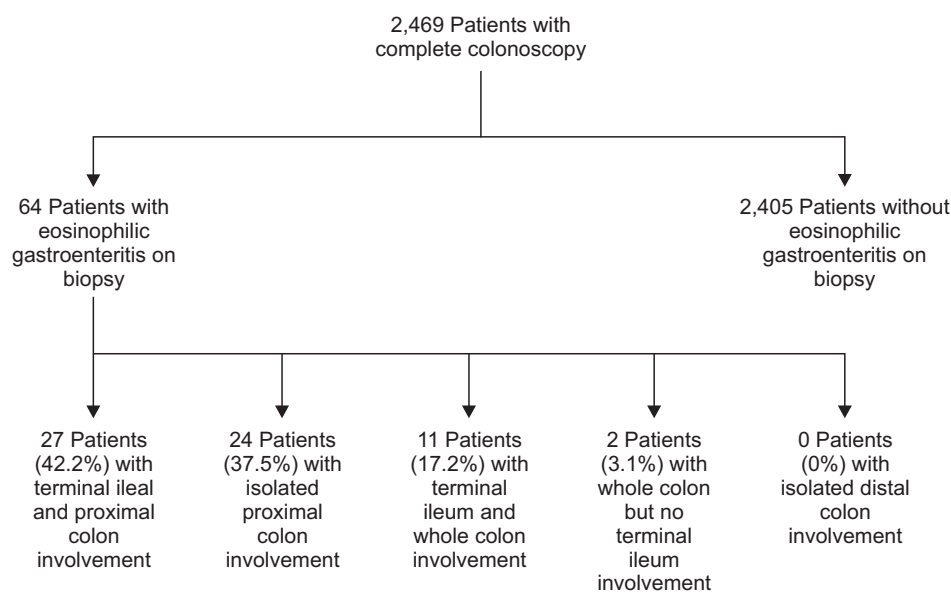

Fig. 1. Study population.

6. Therapy

All patients diagnosed with eosinophilic gastroenteritis were commenced on montelukast 10 mg nocte and ketotifen. The ketotifen was started at 1 mg daily for 1 week and then increased to 1 mg twice daily in the second week, and further increased to 2 mg twice daily from the third week onwards. The drugs were maintained for a period of 16 weeks.

Those without symptomatic relief after 2 to 3 weeks of the above therapy would be commenced on systemic steroid, prednisolone at 0.5 mg/kg daily. The systemic steroid was slowly tapered off after remission of symptoms was achieved for 2 to 4 weeks. The tapering of the systemic steroid was scheduled over a 12 to 16 weeks period by decreasing the dosage by 5 mg per week. Once a dose of 10 mg daily was reached, the systemic steroid was then reduced by 2.5 mg every week.

Table 1. Baseline Characteristics of the Patients with and without Eosinophilic Gastroenteritis

Characteristic	Patients with eosinophilic gastroenteritis (n=64)	Patients without eosinophilic gastroenteritis (n=2,405)	p-value
Age, yr	45 (17–64)	50 (17–81)	<0.001
Sex, male:female	40:24	1,399:1,006	0.498
Presenting symptom			
Diarrhea	30 (46.9)	614 (25.5)	<0.001
Abdominal pain or discomfort	23 (35.9)	504 (14.7)	0.008
Change in bowel habit with increased frequency of bowel motion	7 (10.9)	299 (21.0)	0.849
Change in bowel habit with decreased frequency of bowel motion	2 (3.1)	171 (7.1)	0.319
Constipation	2 (3.1)	154 (6.4)	0.433
Mucous in stool	0	16 (0.7)	1.000
Per rectal bleeding	0	422 (17.5)	0.003
Tenesmus	0	225 (9.4)	<0.001
Endoscopic mucosal abnormality	5 (7.8)	150 (6.2)	0.597
Colitis	3 (4.7)	91 (3.8)	
Ulcers/erosions	1 (1.6)	31 (1.3)	
Hyperemic mucosa	1 (1.6)	28 (1.2)	
Allergic disease	21 (32.8)	654 (27.2)	0.322
Asthma	11 (17.2)	313 (13.0)	0.346
Autoimmune disease	0	36 (1.5)	1.000
Symptom duration, mo	3 (1–36)	3 (1–45)	0.334
Histological findings			-
Adenomas	5 (7.8)	646 (26.7)	
Nonspecific colitis	-	152 (6.3)	
Inflammatory bowel disease	-	39 (1.6)	
Cancer of colon	-	8 (0.3)	
NSAID induced enteropathy	-	2 (0.1)	
Solitary rectal ulcer	-	3 (0.1)	
Microscopic colitis	-	3 (0.1)	
Final diagnosis			-
Irritable bowel syndrome	-	1,371 (57.0)	
Colonic polyp	-	599 (24.9)	
Hemorrhoids	-	401 (16.7)	
Inflammatory bowel disease	-	20 (0.8)	
Cancer of colon	-	8 (0.3)	
Solitary rectal ulcer	-	3 (0.1)	
Microscopic colitis	-	3 (0.1)	

Data are presented as median (range) or number (%).
NSAID, nonsteroidal anti-inflammatory.

This study was approved by the Institutional Review Board of the Centre for Digestive Diseases (Protocol approval number: CDD09-00001). Written consent was obtained from all patients for the first stage of the study, which was to determine the prevalence of eosinophilic gastroenteritis in our cohort. An additional written consent was obtained from those diagnosed with eosinophilic gastroenteritis for the second stage of the study which included further investigation, treatment and follow-up. Those without eosinophilic gastroenteritis on biopsies were referred to other clinics or specialists for further management.

The primary outcome was to determine the prevalence of eosinophilic gastroenteritis. The secondary outcomes were to determine: (1) the extent of disease and (2) factors associated with systemic steroid therapy.

7. Statistical analysis

All statistical analyses were performed using the SPSS software version 20.0 (IBM Corp, Armonk, NY, USA). Mann-Whitney U-test was used for continuous variables with skewed distribution and chi-square with Yates' correction factor or Fisher exact test for categorical variables. Continuous variables were expressed as median (range). Variables were analyzed in a univariate analysis in order to determine any factors associated with upper gastrointestinal involvement, complications or severe disease at the time of presentation and need for systemic steroid treatment. Variables with a p-value ≤0.10 in the univariate analysis were included in a logistic regression analyses to define factors independently associated with upper gastrointestinal tract involvement, complications or severe disease at the time of presentation and the need for systemic steroid treatment. All statistics were performed on the intention to treat the population. Statistical significance was defined as p<0.05 (two-tailed).

RESULTS

1. Study population

A total of 2,477 consecutive Chinese patients underwent colonoscopy during the study period. However, eight of the 2,477 patients (0.3%) had incomplete colonoscopy and they were excluded from the analysis. Therefore, only 2,469 patients were included in the final analysis.

Sixty-four of these 2,469 patients (2.6%) were found to have eosinophilic gastroenteritis on biopsies (Fig. 1). None of these 2,469 patients (0%) developed post-colonoscopy complications such as bleeding or perforation.

The characteristics of patients with and without eosinophilic gastroenteritis are shown in Table 1. Patients with eosinophilic gastroenteritis were significantly younger (p<0.001) and were more likely to present with diarrhea (p<0.001) or abdominal pain (p=0.008) when compared with patients without eosinophilic gastroenteritis. On the other hand, those with eosinophilic
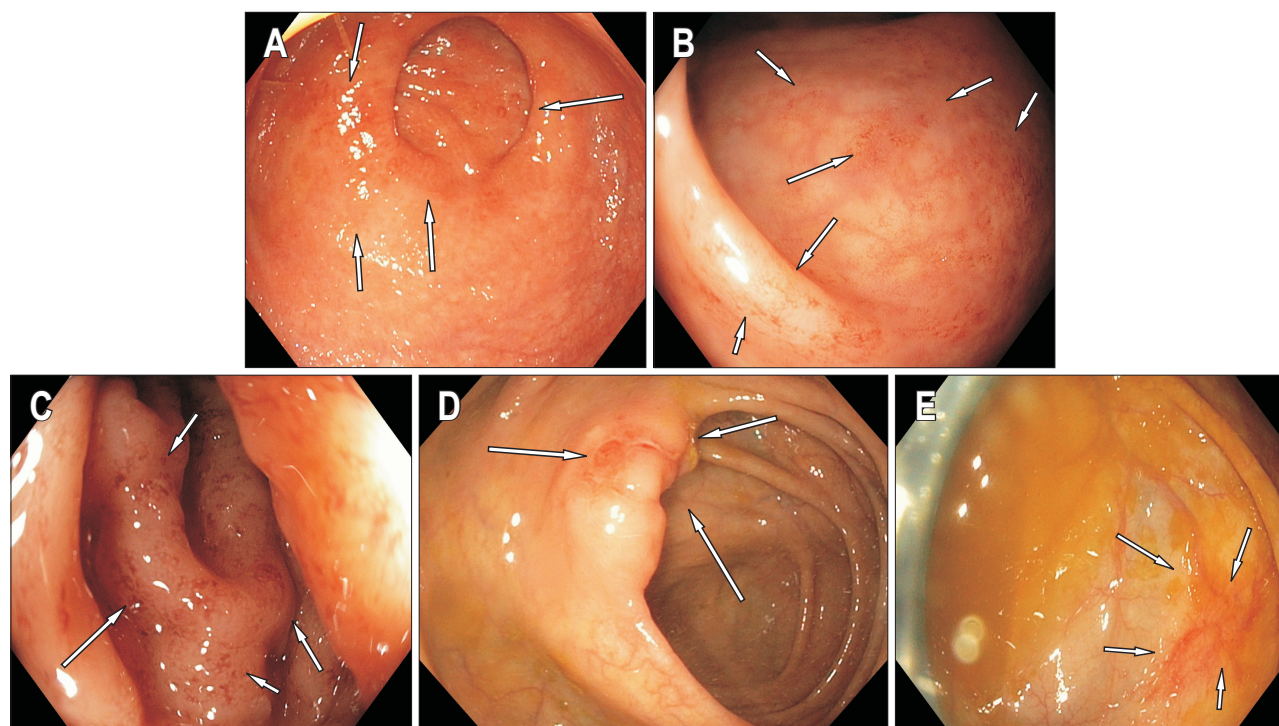

Fig. 2. Endoscopic findings in the five patients with mucosal abnormalities, as seen on colonoscopy (arrows). (A) Endoscopic view showing colitis at the rectum, (B) endoscopic view showing colitis at the descending colon, (C) endoscopic view showing colitis at the transverse colon, (D) endoscopic view showing ulceration and erosion at the ileocecal valve, and (E) endoscopic view showing a hyperemic mucosa at the cecum.

gastroenteritis were less likely to present with per rectal bleeding (p=0.003) or tenesmus (p<0.001) when compared with patients without eosinophilic gastroenteritis.

Diarrhea was the most common indication for colonoscopy in both groups, followed by abdominal pain or discomfort, change in bowel habit, and others. Only five of the 64 patients (7.8%) with eosinophilic gastroenteritis had endoscopic mucosal abnormality during colonoscopy. Three of these patients (4.7%) had colitis, one patient (1.6%) had ulcers/erosions and one patient (1.6%) had hyperemic mucosa (Fig. 2).

Correspondingly, in those without eosinophilic gastroenteritis, 150 of the 2,405 patients (6.2%) had the similar endoscopic mucosal abnormality detected during colonoscopy. In these 150 patients, 91 patients (3.8%) had colitis, 31 patients (1.3%) had ulcers/erosions and 28 patients (1.2%) had hyperemic mucosa.

There was no difference in the number of patients with endoscopic mucosal abnormality on colonoscopy when patients with eosinophilic gastroenteritis were compared with patients without eosinophilic gastroenteritis (p=0.597).

There were no significant differences in sex, allergic disease, asthma, autoimmune disease or symptom duration between those with and without eosinophilic gastroenteritis (all p=NS).

2. Baseline biochemical characteristics of those with eosinophilic gastroenteritis

The baseline biochemistry of the 64 patients with eosinophilic gastroenteritis is shown in Table 2. Two of the 64 patients (3.1%) with eosinophilic gastroenteritis had an absolute peripheral eosinophil count of more than 1.5×10^9/L. Their bone marrow aspirate and trephine showed no evidence of hypereosinophilic syndrome and was in favor of a peripheral cause for the eosinophilia.

Three of the 64 patients (4.7%) were positive for perinuclear-ANCA. However, none of these 64 patients (0%) was positive for cytoplasmic-ANCA. All three patients were assessed by the same rheumatologist and none of them were found to be suffering from ANCA-associated vasculitis or glomerulonephritis, or eosinophilic granulomatosis.

Twenty-five of the 64 patients (39.1%) had thickened colonic

wall (n=21) or mural thickening in the proximal small bowel (n=4) on computerized tomography of the abdomen and pelvis. No patient had ascites.

3. Sites in the colon or terminal ileum with increased eosinophil infiltrate and symptom

According to our biopsy results, the three most common sites in the lower gastrointestinal tract found to be infiltrated by eosinophils were in the terminal ileum and proximal colon (27

Table 2. Biochemical Characteristics of Patients with Eosinophilic Gastroenteritis

Characteristic	Eosinophilic gastroenteritis (n=64)
Hemoglobin, g/dL	13.9 (8.7–16.2)
Platelet, $\times 10^9$/L	242 (127–559)
Total white cell count, $\times 10^9$/L	6.2 (3.4–10.9)
Absolute peripheral eosinophil count, $\times 10^9$/L	0.2 (0–3.5)
Erythrocyte sedimentation rate, mm/hr	14 (1–68)
Albumin, g/L	41 (34–49)
Globulin, g/L	32 (24–40)
Aspartate aminotransaminase, U/L	19 (11–235)
Alanine aminotransaminase, U/L	28 (11–110)
Alkaline phosphatase, U/L	85 (57–155)
Serum immunoglobulin E level, kIU/L	78 (5–1,319)
Positive perinuclear-ANCA	3 (4.7)
Positive cytoplasmic-ANCA	0
Positive anti-nuclear antibodies	2 (3.1)
Elevated serum immunoglobulin E level	36 (56.3)
Elevated absolute peripheral eosinophil count	7 (10.9)
Abnormality detected on computerized tomography of abdomen and pelvis (plain and contrast)	25 (39.1)
Thickened colonic wall	21 (32.8)
Mural thickening of proximal small bowel	4 (6.3)

Data are presented as median (range) or number (%).
ANCA, anti-neutrophilic cytoplasmic antibody.

Table 3. Major Symptoms and Sites in the Gastrointestinal Tract Found to Have Eosinophil Infiltration or Involvement

Presenting symptom	Terminal ileum and proximal colon involvement	Isolated proximal colon involvement	Terminal ileum and whole colon involvement	Whole colon but no terminal ileum involvement	Upper gastrointestinal tract involvement
Diarrhea (n=30)	13	12	3	2	3
Abdominal pain or discomfort (n=23)	11	7	5	0	6
Change in bowel habit with increased frequency of bowel motion (n=7)	3	2	2	0	0
Change in bowel habit with decreased frequency of bowel motion (n=2)	0	1	1	0	0
Constipation (n=2)	0	2	0	0	0

Table 4. Characteristics of the Patients with and without Upper Gastrointestinal Tract Involvement, Complications or Severe Disease at the Time of Presentation and Systemic Steroid Treatment

Characteristic	Upper gastrointestinal tract involvement			Complications or severe disease at presentation			Systemic steroid		
	Yes (n=9)	No (n=55)	p-value	Yes (n=6)	No (n=58)	p-value	Yes (n=7)	No (n=57)	p-value
Age, yr	46 (31–61)	45 (17–64)	0.563	46 (34–61)	45 (17–64)	0.609	46 (34–61)	45 (17–64)	0.867
Sex, male:female	3:6	37:18	0.069	3:3	37:21	0.664	4:3	36:21	1.000
Hemoglobin, g/dL	12.3 (8.7–16.2)	13.9 (9.9–16.2)	0.012	12.9 (9.6–14.9)	13.9 (8.7–16.2)	0.187	13.4 (9.6–14.9)	13.9 (8.7–16.2)	0.382
Platelet, ×10^9/L	286 (210–559)	238 (127–433)	0.060	227 (196–286)	242 (127–559)	0.618	251 (196–286)	238 (127–559)	0.816
Total white cell count, ×10^9/L	6.2 (3.4–9.8)	6.2 (3.7–10.9)	0.521	5.6 (5.2–6.2)	6.2 (3.4–10.9)	0.456	5.9 (5.2–6.6)	6.2 (3.4–10.9)	0.534
Eosinophil count, ×10^9/L	0.4 (0.1–3.5)	0.2 (0–3.3)	0.031	1.0 (0–1.4)	0.2 (0–3.5)	0.206	0.8 (0–1.4)	0.2 (0–3.5)	0.266
Erythrocyte sedimentation rate, mm/hr	14 (2–42)	14 (1–68)	0.982	8 (1–42)	14 (2–68)	0.841	5 (1–42)	14 (2–68)	0.567
Albumin, g/L	37 (34–47)	42 (37–49)	0.025	36 (30–47)	41 (36–49)	0.010	38 (30–47)	41 (36–49)	0.074
Globulin, g/L	33 (24–39)	32 (25–40)	0.974	34 (28–39)	32 (24–40)	0.638	32 (28–39)	33 (24–40)	0.846
Aspartate aminotransaminase, U/L	18 (11–27)	19 (12–235)	0.644	25 (12–235)	19 (11–35)	0.003	27 (12–235)	19 (11–35)	0.005
Alanine aminotransaminase, U/L	28 (11–54)	27 (12–110)	0.490	37 (18–110)	27 (11–75)	0.005	52 (18–110)	26 (11–75)	0.002
Alkaline phosphatase, U/L	79 (57–118)	85 (58–155)	0.485	107 (72–155)	85 (57–149)	0.042	97 (72–155)	84 (57–149)	0.043
Serum immunoglobulin E level, kIU/L	294 (11–446)	67 (5–1,319)	0.286	81 (26–294)	74 (5–1,319)	0.896	188 (26–380)	71 (5–1,319)	0.674
Positive p-ANCA	0	3 (5.5)	1.000	0	3 (5.2)	1.000	0	3 (5.3)	1.000
Positive anti-nuclear antibodies	1 (11.1)	1 (1.8)	0.263	0	2 (3.5)	1.000	0	2 (3.5)	1.000
Elevated serum immunoglobulin E level	5 (55.6)	21 (8.2)	0.467	1 (16.7)	25 (43.1)	0.387	2 (28.6)	24 (42.1)	0.691
Elevated eosinophil count	4 (44.4)	3 (5.5)	0.006	4 (66.7)	3 (5.2)	0.001	4 (57.1)	3 (5.3)	0.002
Presence of isolated colitis	0	9 (16.4)	0.008	1 (16.7)	25 (43.1)	0.387	2 (28.6)	24 (42.1)	0.691
Presence of terminal ileum involvement	9 (100.0)	0	0.008	5 (83.3)	33 (56.9)	0.387	5 (71.4)	33 (57.9)	0691
Upper gastrointestinal tract involvement	–	–		3 (50.0)	3 (5.5)	0.032	3 (42.9)	6 (10.5)	0.052
Complications or severe disease at time of presentation	–	–		–	–	–	6 (87.5)	0	<0.001

Data are presented as median (range) or number (%).
p-ANCA, perinuclear anti-neutrophilic cytoplasmic antibody.

of the 64 patients [42.2%]), followed in descending order by isolated proximal colon involvement (24 of the 64 patients [37.5%]), and, the terminal ileum and whole colon (both proximal and distal colon) involvement (11 of the 64 patients [17.2%]) (Fig. 1).

Only two of the 64 patients (3.1%) had involvement of the whole colon (proximal and distal colon) but without terminal ileum involvement while no patient had isolated distal colon involvement (0 of the 64 patients [0%]) (Fig. 1).

The presenting symptom and sites of eosinophil involvement or infiltration is shown in Table 3.

4. Upper gastrointestinal tract involvement

On OGD, nine of the 64 patients (14.1%) with eosinophilic gastroenteritis had involvement of upper gastrointestinal tract. Five of the 64 patients (7.8%) had isolated involvement of the duodenum while two of the 64 patients (3.1%) had isolated involvement of the esophagus. One of the 64 patients (1.6%) had involvement of both the esophagus and antrum, while one of the 64 patients (1.6%) had involvement of both the antrum and duodenum.

The characteristics of the patients with and without upper gastrointestinal involvement are shown in Table 4. Those with upper gastrointestinal tract involvement were more likely to have a lower serum hemoglobin level (p=0.012), a higher absolute peripheral eosinophil count (p=0.031) and a lower serum albumin level (p=0.025) when compared with those without upper gastrointestinal tract involvement on univariate analysis.

Those with upper gastrointestinal tract involvement were also more likely to have an elevated absolute peripheral eosinophil count (p=0.006) when compared with those without upper gastrointestinal tract involvement.

All nine patients (100%) with upper gastrointestinal tract involvement had terminal ileal involvement when compared with none of the 55 patients (0%) without upper gastrointestinal tract involvement (p=0.008). Patients with upper gastrointestinal involvement were less likely to have isolated colonic involvement when compared with patients without upper gastrointestinal tract involvement (0/9 [0%] vs 9/55 [16.4%], p=0.008).

An elevated absolute peripheral eosinophil count was the only independent factor associated with upper gastrointestinal tract involvement (p=0.036; odds ratio [OR], 8.586; 95% confidence interval [CI], 1.146 to 64.328) on multiple analyses.

5. Complications or severe disease at the time of presentation

Six of these 64 patients (9.4%) had the following complications or severe disease at the time of presentation. One patient presented with acute abdominal pain due to acute cholecystitis, which was treated with laparoscopic cholecystectomy. On histology, the resected gallbladder wall showed transmural congestion with mixed inflammatory infiltration. The gallbladder wall was edematous and infiltrated with many eosinophils.

Three patients had protein-losing enteropathy with low serum albumin level of 30, 31, and 31 g/L, respectively (normal range, 35 to 50 g/L) with concurrent ankle edema at the time of presentation. The sites in the gastrointestinal tract found to be infiltrated by eosinophils in these three patients were terminal ileum and proximal colon; terminal ileum and whole colon; and terminal ileum, proximal colon and duodenum.

Two patients had periportal edema on computerized tomography of the abdomen and pelvis (plain and contrast) and raised liver biochemistry at the time of presentation.

Those with complications or severe disease at the time of presentation had higher serum aspartate aminotransaminase level (p<0.001), higher serum alanine aminotransaminase level (p<0.001) and higher serum alkaline phosphatase level (p=0.042) when compared with patients without complications or severe disease at the time of presentation (Table 4). Patients with complications or severe disease at the time of presentation were also more likely to have elevated absolute peripheral eosinophil count (p=0.001) and upper gastrointestinal involvement (p=0.032) when compared with patients without complications or severe disease at the time of presentation (Table 4).

Elevated absolute peripheral eosinophil count (p=0.005; OR, 25.320; 95% CI, 2.628 to 243.910) was an independent factor associated with complications or severe disease at the time of presentation on multiple analyses.

6. Systemic steroid treatment

Fifty-seven of the 64 patients (89.1%) responded to combination montelukast and ketotifen. Only seven of the 64 patients (10.9%) failed to respond to combination montelukast and ketotifen. Five of these patients had persistent diarrhea while the remaining two had persistent abdominal pain despite 2 weeks of montelukast plus ketotifen.

These seven patients were commenced on systemic steroid treatment and all responded to systemic steroid treatment. The characteristics of these patients are shown in Table 4.

Patients who required systemic steroid treatment had higher serum aspartate aminotransaminase level (p=0.005), higher serum alanine aminotransaminase level (p=0.002), and, higher serum alkaline phosphatase level (p=0.043) when compared with those who did not require systemic steroid treatment (Table 4). Patients who required systemic steroid treatment were also more likely to have elevated absolute peripheral eosinophil count (p=0.002) and had complications or severe disease at the time of presentation (p<0.001) when compared with those who did not require systemic steroid treatment (Table 4).

Complications or severe disease at the time of presentation was independently associated with the use of systemic steroid treatment (p=0.008; OR, 18.021; 95% CI, 2.163 to 150.152) on multiple analyses.

DISCUSSION

To our knowledge, this is the first ever study on the prevalence of eosinophilic gastroenteritis that has been prospectively performed using multiple biopsies taken on all patients undergoing colonoscopy for lower abdominal symptoms. By performing multiple random biopsies, this study provides a relatively more accurate method of determining the true prevalence of eosinophilic gastroenteritis. Therefore, with a prevalence of 2.6%, this study demonstrates that eosinophilic gastroenteritis may not be as uncommon as previously believed.

This study also shows that the majority of patients with eosinophilic gastroenteritis (92.2%) would usually have a normal endoscopic appearance during colonoscopy. Therefore, if biopsies were only taken in those with an abnormal endoscopic appearance, 92.2% of patients with eosinophilic gastroenteritis would have been missed.

A similar observation was reported by Wong et al.[10] In their study, they found that more than half of their endoscopic biopsies which were histologically positive for eosinophilic gastroenteritis were from normal looking mucosa at endoscopy.[10] This lack of mucosal abnormality on endoscopy may explain why the number of cases diagnosed with eosinophilic gastroenteritis remain low, thus limiting our understanding of this disease when compared with other forms of inflammatory colitis such as inflammatory bowel disease even 80 years after it was first described.

Another important finding in this study is that eosinophilic gastroenteritis in our locality usually involves the proximal colon with or without terminal ileum involvement. No patient had an isolated distal colonic involvement. Therefore, one should consider taking biopsies from at least the terminal ileum and proximal colon in those with unexplained refractory lower abdominal symptoms in order to exclude eosinophilic gastroenteritis.

In this series, only 10.9% of those with eosinophilic gastroenteritis had an elevated peripheral eosinophil count on presentation. Those with a raised absolute peripheral eosinophil count were more likely to have upper gastrointestinal involvement.

Although only 9.4% had complications or severe disease at the time of presentation, those with an elevated absolute peripheral eosinophil count were more likely to have complications or severe disease at the time of presentation. This finding is important as it was also found that those with complications or severe disease at the time of presentation would have a higher chance of requiring systemic steroid treatment.

At the time of writing, there is still no consensus on the optimum treatment for eosinophilic gastroenteritis. Systemic steroid remains the cornerstone of any therapeutic therapy, as newly diagnosed patients are usually responsive to systemic steroid treatment.[1,2,10] However, systemic steroid is associated with a variety of undesirable long-term side effects. When the undesirable

long-term side effects of systemic steroid and the evolutionary pattern of eosinophilic gastroenteritis are taken into consideration, clinicians may hesitate to commence systemic steroid on every patient diagnosed with eosinophilic gastroenteritis.

This is because Pineton de Chambrun et al.[15] had found that of all the patients with eosinophilic gastroenteritis, almost half (~42%) had spontaneous remission. In view of such a high spontaneous remission rate, it is easy to understand why clinicians may be reluctant to commence systemic steroid on every patient with eosinophilic gastroenteritis as the risk of the side effects of systemic steroid may outweigh its benefits, especially in those with mild symptoms.

It is with the evolutionary patterns of eosinophilic gastroenteritis in mind that we commenced our patients on combination montelukast[16,17] and ketotifen,[18,19] rather than systemic steroid as the initial therapy. However, 10.9% of our patients required treatment with systemic steroid. As our study has found that the presence of complications or severe disease at the time of presentation is an independent factor associated with the need for systemic steroid therapy, systemic steroid should be considered as the initial therapy in those who has complications or severe disease at the time of presentation.

Among the various forms of eosinophilic gastrointestinal diseases, isolated involvement of the large intestine or colon, categorized as eosinophilic colitis, is the most uncommon form.[9,14,20-22] In this study, 26 of the 64 patients had eosinophilic colitis.

As only a limited number of cases of patients with eosinophilic involvement of the large intestine or colon have been reported in the past 10 years, it is uncertain if they had disease in other segments of the gastrointestinal tract.[9,14,20-22] We have found that in our population, isolated involvement of the large intestine or colon mostly occur in the proximal colon. And, those with isolated large intestine or colonic involvement had a lower chance of developing upper gastrointestinal disease on univariate analysis. However, such an association was not found on multiple analyses.

Our study also showed that those with isolated large intestine or colonic involvement did not have a lower chance of developing complications or severe disease at the time of presentation or a decreased risk of requiring systemic steroid treatment (Table 4). This supports the previous findings that adults with isolated eosinophilic colitis do not have a better prognosis or a milder form of disease when compared with other forms of eosinophilic gastroenteritis.[9,14,20-22]

However, this study has several limitations. Firstly, eosinophilic gastroenteritis is a patchy disease. Cases may be missed due to the limited amount of biopsies that were taken. Secondly, as this is a prospective study on those with lower abdominal symptoms undergoing colonoscopy, we are uncertain of the prevalence of disease in those with upper gastrointestinal symptoms. Thirdly, as all our patients were commenced on combination montelukast and ketotifen, we are unable to determine the

number of patients with self-limiting disease or the proportion of patients with spontaneous resolution. Finally, as patients without eosinophilic gastroenteritis were not followed up, we do not have any data on their treatment regimen and whether their symptom responded to treatment.

In conclusion, the prevalence of eosinophilic gastroenteritis is more common than previously believed and the commonest site of involvement is in the terminal ileum and proximal colon. People with eosinophilic gastroenteritis would usually have a normal looking mucosa on colonoscopy. Finally, systemic steroid treatment should be considered as an initial therapy for those who are having complications or severe disease at the time of presentation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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