ORIGINAL ARTICLE

Eosinophilic gastroenteritis: Clinical profiles and treatment outcomes, a retrospective study of 18 adult patients in a Singapore Tertiary Hospital

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ABSTRACT

Background: Eosinophilic gastroenteritis (EG) can mimic symptoms of common gastrointestinal (GI) disorders but responds well to appropriate treatment. Accurate diagnosis is central to effective management. Data on EG in Southeast Asia is lacking. We aim to describe the clinical profiles and treatment outcomes of adult patients with EG in a Singapore Tertiary Hospital.

Materials and Methods: This retrospective study involved archival search of patients with GI biopsies that showed eosinophilic infiltration from January 2004 to December 2012. Patients' clinical data from computerised hospital records and clinical notes was reviewed. Diagnostic criteria for EG included presence of GI symptoms with more than 30 eosinophils/high power field on GI biopsies. Patients with secondary causes for eosinophilia were excluded.

Results: Eighteen patients with EG were identified (mean age 52 years; male/female: 11/7). Fifteen patients (83%) had peripheral blood eosinophilia. Seven patients (39%) had atopic conditions. Most common symptoms were diarrhoea and abdominal pain. Small intestine was the most common site involved. Endoscopic finding was non-specific. Ten patients were treated with corticosteroids (nine prednisolone, one budesonide): eight patients (89%) responded clinically to prednisolone but four patients (50%) relapsed following tapering-off of prednisolone and required maintenance dose. One patient each responded to diet elimination and montelukast respectively. Half of the remaining six patients who were treated with proton-pump inhibitors, antispasmodic or antidiarrheal agents still remained symptomatic.

Conclusion: Prednisolone is an effective treatment though relapses are common. Small intestine is most commonly involved. EG should be considered in the evaluation of unexplained chronic recurrent GI symptoms.

KEY WORDS:
Chronic diarrhoea; eosinophilia; prednisolone

INTRODUCTION

Eosinophilic gastroenteritis (EG) is a rare primary gastrointestinal disorder characterised by eosinophilic infiltration into one or more layers of the gastrointestinal (GI) tract.[1,2] It may involve any area of GI tract from oesophagus to the rectum, although the stomach and proximal small intestines are most commonly affected.[3-5] EG has been found to affect all age groups but usually presents in the third to fifth decades of life and has a slight male preponderance.[5-7]

Though firstly described in 1937 by Kaijser,[8] the aetiology and pathogenesis still remain elusive. In 1984, Oyaizu *et al.* demonstrated evidence for the hypothetical IgE-induced, mast cell mediated allergic mechanism in EG.[9] Recent investigations strongly suggest a role for eosinophils, chemokines such as eotaxin and Th2 proinflammatory cytokines namely interleukin (IL)-3, IL-5 and IL-13 as the pivotal factors in the Th2-driven immune activation, leading to eosinophilic inflammation of the GI tract.[4,10]

Klein *et al.* classified this disorder into three major pathological types based on the depth of tissue involvement (mucosa, muscle or subserosal layers), which determined the varied clinical manifestations.[11] Chang *et al.* and Talley *et al.* assessed the clinical spectrum based on this classification in two of the largest series to date.[5,6] Due to the heterogeneous clinical presentation which can mimic or overlap with other common GI disorders such as irritable bowel syndrome (IBS), the diagnosis of EG remains a challenge to physicians. Corticosteroids have been shown to be effective therapeutically.[6] Hence, high index of clinical suspicion is warranted for accurate diagnosis of EG as appropriate treatment could lead to clinical improvement. The current accepted diagnostic criteria for EG includes presence of GI symptoms, histological evidence of significant eosinophilic infiltration of the GI tract and the absence of parasitic or extraintestinal diseases that may cause eosinophilia.[5-7,12]

The epidemiology and the disease burden of EG remain obscure and challenging to assess given the rarity of the incidence and hence the relative dearth of large prospective studies. Although case series from the United States (US),[5,6] Europe,[13,14] and Asia[12,15-22] have been reported, the clinical data for EG particularly in Southeast Asia remains scanty. In this study, we sought to describe the clinical profiles of adult patients with EG in Singapore General Hospital, the largest tertiary hospital in Singapore.

This article was accepted: 6 July 2015
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MATERIALS AND METHODS

This retrospective study involved archival search of patients with GI biopsies that showed eosinophilic infiltration from January 2004 to December 2012 at the Department of Pathology. The histological slides were reviewed by two experienced consultant GI histopathologists. The diagnostic histological criteria for EG were eosinophilic infiltration of the lamina propria of the intestinal walls (>30 eosinophils per high-power field [x400] on optical microscopy) (Fig. 1) associated with one or more of the other histopathological features such as eosinophilic microabscesses, eosinophilic cryptitis and extension of eosinophilic infiltration into the submucosa.[5-7]

Clinical data of patients who fulfilled the histological criteria of EG was then reviewed via computerised hospital records and clinical notes to verify the clinical diagnosis of EG i.e with the presence of GI symptoms without evidence of secondary aetiologies for eosinophilia. Subjects were excluded if they were diagnosed as follows: eosinophilic esophagitis, parasitic infestation or clinical response to empirical anti-parasitic agents if stool tests for ova cysts and parasites were negative, hypersensitive reaction to drugs, inflammatory bowel disease, malignancy, lymphoma, autoimmune disease and hypereosinophilic syndrome.

Data collected from the records included patients' demographics, presenting symptoms and signs, drug and allergy history (atopy, asthma, urticaria/hay fever), food allergy panels, stool tests for ova cysts and parasites, blood investigations including absolute eosinophil counts, serum albumin and IgE, endoscopic and radiological findings, sites and histology of GI biopsies, treatment outcomes and follow-up duration until 31 December 2012.

Data were analysed using SPSS (Statistical Packages for the Social Sciences, version 21, Chicago, IL, USA). Comparison between proportions was performed using Fischer's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

Ninety patients with eosinophilic infiltrates on GI biopsies were identified. Eighteen patients fulfilled the diagnostic criteria for EG. The demographics and clinical data of these 18 patients are summarised in Table I. The median duration from onset of symptoms to diagnosis was 1.5 month (range, 0.5-49 months). Serum IgE was performed in 11 patients and 10 of them (91%) had elevated levels ranging from 164 to 3165 IU/ml. (Normal range <100 IU/ml). Food allergy panel was performed in 2 patients. One patient showed positive reaction to shrimp.

More than two-third of the patients had combined gastroscopy and colonoscopy. Biopsies were taken from different sites along the GI tract. Distribution of biopsy specimen taken at each site of GI tract and the proportion of patients with positive histology at each site were shown in Table II. Small bowel (23/28, 82.1%) was the most common site affected as compared to oesophagus (1/3, 33.3%), stomach (2/14, 14.3%) and colon (9/17, 52.9%), $p<0.05$ for all comparisons. Thirteen out of 18 patients (72.2%) had at least 2 different sites of GI tract involvement. The endoscopic findings were non-specific. Sixty percent (21/35) of the positive biopsies correlated with normal mucosal appearance on endoscopy (Table II). Abnormal endoscopic findings included most commonly hyperaemic mucosa followed by erosions, ulcers, and whitish lesions. Significant eosinophilic infiltration was found in the mucosa (lamina propria) in all patients and in the submucosa in 6 patients. Computer tomography (CT) scan of the abdomen was performed in 16 patients. Six patients (37.5%) had abnormal findings. One patient had thickened colonic wall. Mural thickening in proximal small bowel (Fig. 2) was observed in 5 patients, making it the most common radiological abnormality. Two of these 5 patients had concomitant ascites. The bowel mural thickening on CT scan correlated with the histological diagnosis of EG.

Types of treatment, follow-up duration and their outcomes were summarised in Table III. Ten of these 18 patients were treated with corticosteroids (nine with prednisolone 30 to 40mg/day, which was tapered gradually over 1 to 3 months, and one with budesonide 9mg daily for 3 weeks). Eight of the 9 patients (88.9%) who were treated with prednisolone had clinical response within few weeks, as evidenced by the improvement or the resolution of GI symptoms and eosinophilic infiltration on repeat endoscopic biopsy. Four patients relapsed following tapering-off of prednisolone (three patients had one episode each and one patient had four episodes) and they required long term low-dose prednisolone (1-5mg/day). One patient was added on with azathioprine for steroid-sparing maintenance. Out of the 10 patients treated with corticosteroids, two patients did not respond clinically (one each to prednisolone and budesonide). The prednisolone-refractory patient presented with protein-losing enteropathy complicated with weight loss and malabsorption with severe hypoalbuminemia and bilateral leg oedema. He was given a trial of ketotifen 1mg bd for 6 months and 2 weeks of total parenteral nutrition (TPN) followed by oral elemental diet. His hypoalbuminemia and leg oedema improved. Repeat endoscopy showed improvement of eosinophilic infiltration on GI biopsies.

One patient had clinical resolution with monteleukast 10mg daily for 1 month. He remained asymptomatic for 10 months before lost to follow-up. The young patient who was tested positive to shrimp on food allergy testing, had clinical improvement with diet elimination. His repeat endoscopy 3 months later showed resolution of eosinophilic infiltrates on GI biopsies. Twelve patients who were identified with EG in our study were diagnosed as such by the primary physicians. The other 6 patients were treated by the initial managing clinicians with different combinations of proton pump inhibitors (PPI), antispasmodic and anti-diarrheal agents and half of them still remained symptomatic.

DISCUSSION

Eosinophils are constitutive inhabitants of the GI tract, except for oesophagus, in the normal and healthy state. Hence, as opposed to eosinophilic esophagitis, diagnosis of EG is more

Table I: Demographics and clinical profiles of patients with EG

Variables	EG patients (n=18)
Mean age at diagnosis, years (range)	52 (21-77)
Sex, %	
Male	61.0
Female	39.0
Ethnicity, %	
Chinese	77.8
Indian	16.7
Malay	5.6
History of allergy, %	38.9
Hypoalbuminemia*, %	66.7
Peripheral eosinophilia, %	83.3
Absolute eosinophil counts ($x10^9$/L), range	1.53-21.8
Presenting symptoms / signs, %	
Diarrhoea	100.0
Abdominal pain/bloating	83.3
Weight loss	38.9
Nausea/vomiting	22.2
Ascites	11.1
Lower limb oedema	5.6
Type of endoscopy performed, %	
Gastroscopy plus colonoscopy	78.0
Colonoscopy alone	11.0
DBE alone	5.5
Gastroscopy plus DBE plus colonoscopy	5.5

* Serum albumin <35g/L; DBE: Double balloon enteroscopy

difficult and challenging.[2,10,23] Uncertainties exist in the histological criteria for EG especially the cut-off number of eosinophilic infiltration in the tissue biopsy. This is largely due to the relative rarity of the disease which precludes well-designed studies and accounts for a lack of consensus to date albeit the limit of ≥ 20/hpf has been widely adopted.[5,6,12] The number of eosinophil infiltration varies along the normal digestive tract. Some sites of the GI tracts especially the small bowel may even exhibit as many as 30 eosinophils/hpf.[10] This may lead to overdiagnosis if 20 eosinophils/hpf were to be used as the cut-off figure. Besides, it is also influenced by age, seasonal and geographical variations, making it a challenge to define a specific number which may differ between pathology departments.[7] We adopted a density of >30 eosinophils/hpf with at least one of the histological features including eosinophilic cryptitis as our criteria for this study as this has been recently proposed to be a more robust criteria as they are less dependant on the variations of age, season, geographical region and sites of tissue biopsy.[7] Though we acknowledge that our histological diagnostic criteria is slightly more stringent and hence some cases may be missed, the largest series reported to date by Chang *et al.* with 59 adult EG patients has found that most of the patients often had ≥ 50 eosinophils/hpf in the tissue biopsies.[6] Thus, the impact on the number of our patients will likely to be minimal.

Table II: Distribution of biopsy specimens and involvement of EG at different sites of GI tract

Site of biopsies	Number of patients biopsied at each site	Proportion of patients with biopsy >30 eosinophils/HPF at each site (%)	H+/E-
Oesophagus	3	1/3 (33.3)	1
Stomach	14	2/14 (14.3)	1
Small bowel*	28	23/28 (82.1)	15
D2	14	11/14 (78.6)	8
Jejunum	2	2/2 (100)	0
TI	12	10/12 (83.3)	7
Colon	17	9/17 (52.9)	4

H+/E- : The number of patients with positive histology for EG but negative endoscopic finding at each site
* Small bowel was divided into second part of duodenum (D2), jejunum and terminal ileum (TI) where the biopsies were taken.

Table III: Treatment responses and clinical outcomes of patients with EG

Patient No	Treatment	Duration of Follow-up (Months)	Clinical Outcomes
1	P + M	36	In remission
2	Others	93	Recurrent symptoms
3	P	15	In remission
4	P	86	1 relapse episode
5	P	68	1 relapse episode
6	Others	34	Recurrent symptoms
7	Others	9	Asymptomatic
8	Others	2	Asymptomatic
9	P	13	In remission
10	Others	8	Recurrent symptoms
11	P + A	126	4 relapse episodes
12	P	73	1 relapse episode
13	P, K + TPN	92	Improved with K + TPN
14	P	33	In remission
15	M	10	Improved
16	Others	5	Asymptomatic
17	D	19	Improved
18	B	17	Recurrent symptoms

A: Azathioprine; B: Budesonide; D: Diet Elimination; K: Ketotifen; M: Montelukast; Others including PPI (proton pump inhibitor), anti-spasmodic and anti-diarrheal agents; P: Prednisolone; TPN: Total parenteral nutrition

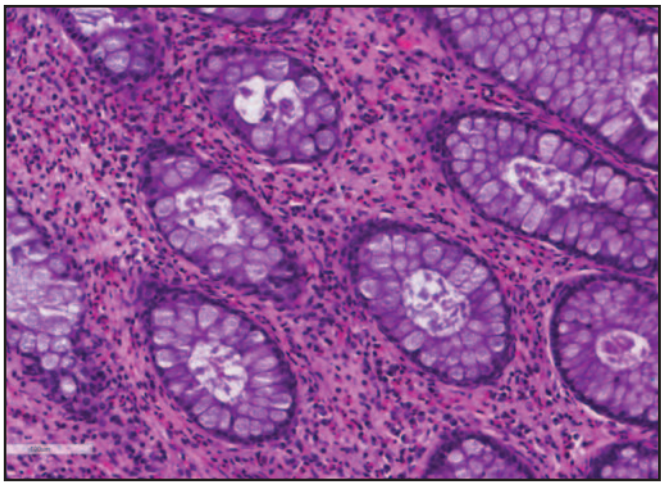

Fig. 1: Photomicrograph of a colonic mucosal biopsy specimen from a patient with EG showing inflammation and dense eosinophilic infiltration in the lamina propria. (hematoxylin and eosin stain, 400x).

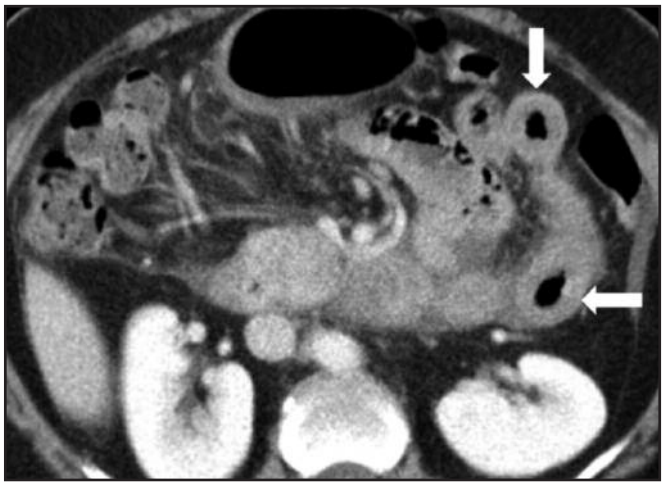

Fig. 2: Axial section from a Computed Tomography of the abdomen performed with intravenous contrast medium showing concentric wall thickening of a segment of the jejunum (white arrows), a relatively common positive radiological finding in our series of patients with EG.

An association between EG and allergic conditions such as asthma and atopy has been proposed.[24] Our study reported that 39% of patients had history of allergy. This is comparable with reports of 20% to 50% from other studies.[6,12,20,21] In patients who had serum IgE level checked, over 90% showed elevated levels, suggesting a possible role of hypersensitivity in the pathogenesis. Peripheral eosinophilia was absent in 17% of our patients and 20-40% in other studies.[5,12,20] Although peripheral eosinophilia is not a universal feature for EG and could be found in parasitic infection, allergic disorders and lymphoma, it may be the first clue for further evaluation of patients with suspected EG. It has been reported that only 30-50% of patients with EG who underwent food allergy testing had a positive finding and there was no apparent over-representation on particular food category.[6,25] This test was performed in 2 patients in our study. Interestingly, one patient who was tested positive for shrimp had clinical resolution with diet elimination. Food allergy testing should be considered in the evaluation of patient with suspected EG especially in children and young adults. Collectively, high index of suspicion for EG is warranted in the context of GI symptoms, peripheral eosinophilia and a history of allergy.

The clinical manifestations of EG may range from mild IBS-like symptoms to acute abdomen due to intestinal obstruction, intussusception, perforation or pancreatitis.[5,6,11–13,15,21,22,26–28] These will depend primarily on the GI tract involvement based on Klein classification. Patient with predominantly mucosal disease present mainly with nausea/vomiting, abdominal pain, diarrhoea, malabsorption, weight loss and protein losing enteropathy. Those with muscular involvement tend to present with bowel thickening and stenosis leading to intestinal obstruction. Serosal involvement will result in eosinophilic ascites. All of our patients exhibited clinical presentation consistent with mucosal involvement. Two patients who had mucosal infiltration may have concurrent serosal and muscular involvement as evidenced by the presence of ascites and bowel thickening on CT abdomen, suggesting that each layers of the gut may be involved simultaneously. The predominant mucosal involvement in our cohort may be skewed by the clinical presentation of patients and the use of endoscopy as the initial diagnostic tool for evaluation and tissue biopsies. On the other hand, this may be due to the shift of clinical spectrum of EG toward the mucosal disease type (90%) as recently described in a recent study in the US.[6] This observation is notably contrary to the previous report 20 years ago, estimating the distribution of EG type at 60% mucosal, 30% muscular and 10% subserosal disease respectively.[5] The authors attributed this shift to earlier assessment with greater use of endoscopy nowadays, hence diagnosis of EG at an earlier stage. It is also postulated that the pathogenesis of EG may extend from mucosa to deeper layers of the GI wall as disease progresses.[6]

Definitive diagnosis of EG requires histological evidence of significant eosinophilic infiltration of GI tract. Unfortunately, eosinophilic infiltration does not always occur in areas with macroscopic abnormalities at endoscopy. Conversely, it may be present in otherwise normal appearing mucosa due to the patchy distribution of EG.[4,5,13] This is consistent with our study which showed that more than half of the endoscopic biopsies positive for EG were from normal looking mucosa at endoscopy.

As previously described, EG may affect any part of the GI tract but small bowel and antrum are commonly affected.[5] However, our study showed that gastric antrum/body were less commonly involved and small intestines were most commonly affected. This is in keeping with other recent studies.[14,21] The endoscopic features of EG are rather non-specific. Therefore, multiple biopsies from normal and abnormal mucosa especially in small intestine are suggested so as to improve the diagnostic yield. Radiographic appearance of EG are not pathognomonic.[2,10,12,29] Thickened bowel wall is a common radiographic finding. Ascites is a recognised radiographic feature if the serosal is involved.

Only three patients in our study had oesophageal biopsies. One patient who had concomitant eosinophilic infiltration in the oesophagus, responded well to prednisolone and montelukast. He was devoid of symptoms typical for eosinophilic esophagitis (EE) i.e., dysphagia or food impaction.[23] The most common symptoms in our patients were abdominal pain and diarrhoea with no oesophageal symptoms, thus oesophageal biopsies were not routinely taken. Therefore, possibilities that concurrent EE might have been missed in some cases. As the incidence of EE has been rapidly rising,[23] oesophageal biopsies should also be considered in the evaluation of EG to exclude concomitant EE.

There is no well-established treatment for EG. Prednisolone remains the cornerstone of therapeutic option. Approximately 89% of our patients treated with prednisolone showed clinical response within a relatively short period of time. This has also been consistently demonstrated in previous studies.[5,6,12,15,20,21] The beneficial effects of steroids are mediated by inhibition of eosinophil growth factors, IL3 and IL5.[7] The appropriate duration of steroid treatment remains uncertain. Most patients receive prednisolone in doses ranging from 20 to 40 mg/day for 6-8 weeks with various schemes of dose tapering.[2] Other alternative therapeutic armamentarium include mast cell stabilizer (oral cromolyn),[6,30] leukotriene antagonist (montelukast),[6,25,31-33] budesonide [34,35] and histamine-1 blocker (ketotifen).[36] Immunotherapy particularly anti-IL-5 monoclonal antibodies has also been adopted in clinical trial but with limited therapeutic effects.[37,38] Data on steroid-resistant EG and the treatment options remain nebulous. As these treatment options have not been proven in randomised studies, they remain off-label prescription based on physician's experience and preference.

The disease course of EG was recently described and spontaneous remission occurred in 40% of patients.[14] In our study, half of the 6 patients who were managed symptomatically without specific treatment, i.e., prednisolone and remained asymptomatic, may have achieved spontaneous remission. However, their follow-up duration was too short to draw a conclusion and 2 of them were lost to follow-up. The other 3 patients who still had recurrent GI symptoms may perhaps benefit from a trial of prednisolone.

EG is increasingly recognised but our knowledge on many aspects of this rare clinical entity is still lacking. Whilst this study could shed some light on the clinical features and treatment outcomes of this rare disease, it is however limited by its small sample size and retrospective nature. Hence, larger, prospective and multicenter studies are needed to better delineate the disease course, optimum management strategies, and long term outcome of these patients.

CONCLUSION

Though rare, EG does occur in Singapore. Patients with EG respond well to prednisolone but relapses are common. Small intestine is the most common site involved. Peripheral eosinophilia and history of allergy may be absent, the disease may be patchy, and may involve different sites of GI tracts, making diagnosis of EG a challenge. Mucosal disease is predominant in our series and may cause symptoms that could masquerade as functional bowel diseases. Hence, clinical vigilance is required for correct diagnosis of EG as corticosteroid may lead to substantial symptom relief. Though EG is a rare disease, it should be considered in the evaluation of unexplained chronic recurrent GI symptoms especially in the presence of peripheral eosinophilia and history of atopy.

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