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Eosinophilic gastrointestinal disorder: is it what it seems to be?

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Abstract

Background Eosinophilic gastroenteropathy is an uncommon condition whose causes can be numerous and non-specific. The aim of the study was to characterize the presence of gastrointestinal disorders in the adult Maltese population and assess the degree of association with atopic diseases.

Methods Adult patients with gastrointestinal eosinophilia in the gastrointestinal tract on histology were identified and their clinical case notes were reviewed. Patients were interviewed and asked questions regarding asthma, allergic rhinitis, and eczema.

Results Sixty-six patients (39 female) were recruited. The most common clinical symptoms were diarrhea (42.4%) and abdominal pain (33.3%). The sites involved were stomach (10.6%), colon (56.1%), small bowel (10.6%), small bowel and colon (18.2%), esophagus (1.5%), and esophagus and colon (1.5%). Forty percent had persistent lower gastrointestinal symptoms and a repeat ileocolonoscopy was performed within 12 months. These patients were diagnosed with ulcerative colitis (n=10; 47.6%), Crohn's disease (n=6; 28.6%), indeterminate colitis (n=1; 4.8%) or microscopic colitis (n=4; 19%). Allergic rhinitis was present in 39.4% of the study group, eczema in 26.1%, and asthma in 19.7%. These findings were compared with local data for atopic conditions and the study group was found to have a significantly higher prevalence of allergic rhinitis (P=0.002), but not of asthma (P=0.62) or eczema (P=0.19).

Conclusions A high proportion of patients with eosinophilic gastrointestinal infiltration were subsequently diagnosed with inflammatory bowel disease. Patients persistently symptomatic or who do not respond to treatment should be reassessed to exclude inflammatory bowel disease, given its high prevalence in this group of patients.

Keywords Eosinophilic esophagitis, eosinophilic gastrointestinal disorders, inflammatory bowel disease, ulcerative colitis, Crohn's disease

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Introduction

Eosinophilic esophagitis and gastroenteritis are chronic inflammatory conditions that occur in response to allergens [1,2]. They are associated with several cytokines, including interleukin (IL)-5 and IL-15 [3,4]. Eotoxin-3 and IL-13 are overexpressed in patients with eosinophilic esophagitis [5]. IL-4 and IL-3 together stimulate the production of exotoxin-3 [6]. In healthy adults, the number of eosinophils (Eo) in the intestinal wall increases from the esophagus to the right colon and decreases again in the left colon [7]. Eosinophilic gastrointestinal enteropathy (EGEs) and the effects of allergies on the gastrointestinal tract were described as early as 1937 in papers by Kaijser, Hansen, Simonsen, Afendoulis and Gulzow [8-10].

Eosinophilic esophagitis is characterized by eosinophilic infiltration (≥15 Eo/high power field [HPF]) and secondary fibrosis [11]. No such consensus exists for eosinophilic colitis. A few studies defined eosinophilic gastroenteritis as an Eo density of ≥30 Eo/HPF [12,13]. However, the most accepted definition of EGE in the rest of the gastrointestinal tract, especially the colon, is an Eo count that exceeds 20 Eo/HPF [14-16].

Epidemiological studies show eosinophilic esophagitis to have a prevalence of 25.9 to 50 patients per 100,000

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Conflict of Interest: None

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inhabitants [17,18]. The prevalences of eosinophilic gastroenteritis, eosinophilic colitis and eosinophilic gastritis are reported to be 5.1-8.4, 2.1-3.3, and 6.3 per 100,000 patients, respectively [15,19]. Adults are more commonly affected than children and people in the fourth to the fifth decades of life are most affected [20,21]. Both eosinophilic esophagitis and gastrointestinal disorders are more common in Caucasian males [22-24].

EGEs can be further subclassified according to the degree of infiltration of Eo in the intestinal wall. Mucosal involvement is the most common subtype. Patients in this subgroup tend to have non-specific gastrointestinal symptoms of nausea, vomiting, abdominal pain and diarrhea [13,25]. Involvement of the muscular layer often leads to symptoms of intestinal obstruction [26] or rarely intussusception [27]. Serosal involvement is uncommon. Patients can present with ascites and intestinal obstruction [28].

In a study by Mansoor *et al*, patients with EGEs were more likely to have been diagnosed with gastrointestinal conditions and allergic disorders [29]. This association might be due to common pathways causing atopic diseases and EGEs. The aim of our study was to characterize the presence of eosinophilic esophagitis and gastrointestinal disorders in the adult Maltese population and assess the degree of association with atopic diseases.

Patients and methods

Patients who had undergone upper gastrointestinal or lower gastrointestinal endoscopy between January 2014 and December 2015 and who had eosinophilic infiltration of the gastrointestinal tract on histology were retrospectively identified through the histopathology database. Inclusion criteria were: 1) patients >18 years of age; 2) the presence of Eo in esophageal, gastric, small bowel and colonic biopsies (defined as eosinophilic infiltration ≥15 Eo/HPF for esophageal involvement and >20 Eo/HPF for the rest of the gastrointestinal tract [14]); and (3) the absence on histological samples of results suggesting another cause of eosinophilia.

Exclusion criteria were: 1) age under 18 years; 2) current and recent infective gastroenteritis (recent being defined as <3 months); 3) previous diagnosis of inflammatory bowel disease (IBD) and/or celiac disease; 4) drug-induced pathologies; 5) graft-versus-host disease; 6) history of connective tissue disorders and/or vasculitis; 7) previous radiotherapy to the abdomen; 8) primary hypereosinophilic syndrome; and 9) myeloproliferative neoplasms.

Patients were then interviewed using a questionnaire to determine their gastrointestinal symptoms at the time of endoscopy and to check if they had symptoms of asthma, allergic rhinitis and/or eczema. All patients had a complete blood count with measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-tissue transglutaminase antibodies. Patients who presented with loose stools had stool samples checked for culture, ova, cysts and parasites, and *Clostridium difficile*. All patients were followed up for a minimum of 12 months post endoscopy.

This study was approved by the Ethics committee of the University of Malta. Informed consent was obtained from all patients.

Statistical analysis

Data was analyzed using SPSS version 21. The main statistical tests used were the Student's *t*-test and the Mann-Whitney *U* test.

Results

Sixty-six patients (39 female; 59.1%) were recruited. The mean patient age was 48.4±18.5 years (Table 1). The most common clinical symptoms that necessitated an endoscopic procedure were diarrhea (42.4%) and abdominal pain (33.3%). Fig. 1 presents the patients' symptoms. Thirteen patients underwent a gastroscopy (19.7%). Fifty-three patients (80.3%) had a colonoscopy because of their preceding symptoms. Only 3 (4.5%) of these patients had bidirectional endoscopy (Table 1).

Table 2 shows the various parts of the gastrointestinal tract with eosinophilic infiltration. The lower gastrointestinal tract was affected as follows: terminal ileum (n=7; 12%); terminal ileum and colon (n=9; 15.5%); terminal ileum and rectum (n=2; 3.4%); terminal ileum and sigmoid colon (n=1; 1.7%); colon (n=20; 34.5%); hepatic flexure (n=1; 1.7%); transverse and sigmoid colon (n=1; 1.7%); transverse colon (n=3; 5.2%); cecum and rectum (n=2; 3.4%); ascending and transverse colon (n=4; 6.9%); ascending colon (n=4; 6.9%); rectum

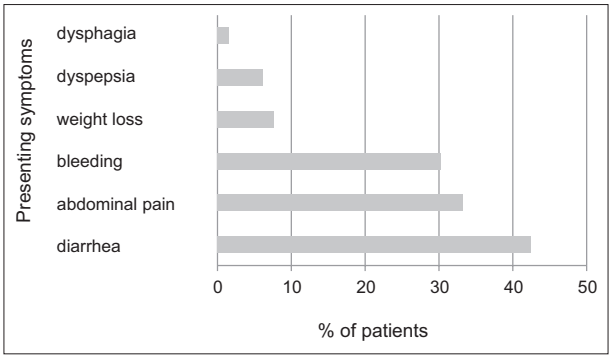

Figure 1 Presenting symptoms vs. percentage of patients

Table 1 Demographic details of patients in this study

Demographics	Number	Percentage
Patients	66	
Female	39	59.1
Mean age (years ± SD)	48.4±18.5	
Gastroscopies	13	19.7
Colonoscopies	53	80.3

SD, standard deviation

(n=2; 3.4%); and cecum (n=2; 3.4%). None of the patients with esophageal eosinophilic infiltration had macroscopic mucosal abnormalities. The patients with stomach eosinophilic infiltration (n=7; 10.6%) had antral erythema at endoscopy. Seven patients (n=51; 13.7%) with colonic eosinophilia had patchy areas of erythema. None of the patients with small bowel involvement had macroscopic endoscopic findings.

The patients with eosinophilic esophageal infiltration were administered inhaled budesonide. Previously they had only used inhaled bronchodilators. Since patients with gastric eosinophilia exhibited erythema at endoscopy, they were prescribed a proton pump inhibitor (PPI) for 6-8 weeks. Their symptoms resolved and did not recur after PPI cessation. Twenty-one patients (n=58; 36.2%) with colonic/terminal ileum eosinophilia were asymptomatic at follow up and did not undergo a repeat colonoscopy. Nine patients (n=58; 15.5%) had a history of acute gastroenteritis more than 3 months before the endoscopy. Symptoms resolved spontaneously. Seven patients (n=58; 12.1%) were lost to follow up.

More than a third of the patients (39.6%) had persistent lower gastrointestinal symptoms and a repeat ileocolonoscopy was performed within 12 months. These patients were all diagnosed with ileocolonic pathologies: ulcerative colitis (UC) (n=10; 47.6%), Crohn's disease (CD) (n=6; 28.6%), indeterminate colitis (n=1; 4.8%) or microscopic colitis (n=4; 19%). Table 3 demonstrates the phenotypic features of the patients with IBD. One patient with ileal CD also had stricturing disease. Nine patients had persistent eosinophilia on repeat histology. All the patients diagnosed with IBD had histological features on biopsy consistent with UC or CD.

The most common blood abnormalities were elevated values of ESR (33.3%) and CRP (100%). The peripheral eosinophil count was only raised in 6.25% of cases. Table 4 shows the blood results. The CRP levels measured prior to the endoscopic procedures were higher in those patients who were later diagnosed with IBD than in the rest of the cohort (10.1 vs. 8.61 mg/L; P=0.029), whereas there was no significant difference in ESR.

Patients were asked about a previous diagnosis of atopic conditions. Allergic rhinitis was reported in 39.4% of patients, eczema in 26.1% and asthma in 19.7% of the study group. These findings were compared with local data for atopic conditions [30] and the study group was found to have a significantly higher prevalence of allergic rhinitis (P=0.002), but not of asthma (P=0.62) or eczema (P=0.19) (Table 5).

With regard to family history (first-degree relatives), 4.5% had a positive family history of IBD. There was no correlation between levels of Eo on histology or peripheral eosinophil count and organ involvement. There were no apparent dietary restrictions and all patients had negative celiac serology.

Table 2 Site of eosinophilic infiltration

Site	Number	%
Stomach	7	10.6%
Colon	37	56.1%
Small bowel	7	10.6%
Small bowel & colon	12	18.2%
Esophagus	1	1.5%
Esophagus & colon	2	3.0%

Table 3 Characteristic features of patients with inflammatory bowel disease (IBD)

Type of IBD	Number of patients	% of patients
Ulcerative colitis		
Left-sided colitis	3	14.2
Pancolitis	7	36.8
Crohn's disease		
Colonic Crohn's	2	9.52
Ileal Crohn's	2	9.52
Ileocolonic Crohn's	2	9.52
Indeterminate colitis	1	4.8
Microscopic colitis	4	19

Discussion

In healthy people, Eo reside in the *lamina propria* of the stomach and intestine [31]. On stimulation, Eo can release eosinophil cationic protein [32], eosinophil protein

Table 4 Blood tests in the cohort of patients with eosinophilic gastrointestinal disorders

Blood test	Mean ± SD	Normal range
White cell count	$7.37\pm2.71 \times 10^9$ /L	$4.3\text{-}11.4 \times 10^9$/L
Hemoglobin	13.2±1.98 g/dL	12-15.5 g/dL
Platelets	$258.0\pm66.9 \times 10^9$ /L	$142\text{-}349 \times 10^9$ /L
ESR	15.0±19.6 mm/h	10-14 mm/h
CRP	9.12±17.2 mg/L	0-5 mg/L
Peripheral eosinophilic count	$0.353\pm1.08 \times 10^9$ /L	$0.00\text{-}0.6 \times 10^9$ /L

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SD, standard deviation

Table 5 Comparison of atopic conditions in this study to data from the 2009 local study [30]

Condition	This study		2009 study		P-value
	% yes	% no	% yes	% no	
Allergic rhinitis	41.3%	58.7%	22.20%	77.8%	0.002
Asthma	17.4%	82.6%	14.80%	85.2%	0.623
Eczema	26.1%	82.6%	11.20%	88.8%	0.186

X [33], eosinophil peroxidase and several proinflammatory cytokines [34-36]. These cytokines attract more inflammatory cells, such as neutrophils, to the intestinal lining [37]. They can also act as antigen-presenting cells, which in turn stimulate T-cell proliferation and activation [38]. This mechanism occurs in patients with active IBD [39-41], atopic conditions such as asthma [42] and EGEs [43]. Eo can be proinflammatory and therefore play a role in tissue destruction in IBD. Their numbers are greatly increased in the intestinal lining of patients with active disease [44-47].

However, they can also play a role in tissue repair. In studies by Lampinen *et al*, the activity of Eo was higher in the inactive than in the active phase of UC and CD [48,49]. Transforming growth factor-β1 and IL-13 derived from Eo promote the transformation of fibroblasts to myofibroblasts, and stimulate the expression of tenascin and procollagen I by these cells in atopy and asthma [50,51]. This is essential for tissue repair.

There are two case series in the literature that report patients initially diagnosed with eosinophilic colitis who did not respond to treatment (elimination diet, anti-histamines, mast cell stabilizers, antibiotics) and who were subsequently histologically diagnosed as having UC [52] or CD [53]. EGEs and IBD might be two distinct disorders with different diagnostic criteria but common clinical manifestations and overlapping pathogenesis. It is therefore not surprising that 25.8% of our patients initially diagnosed with EGEs were later diagnosed with IBD. This aspect raises the question of whether patients with EGEs should undergo repeat endoscopy when they fail to respond to treatment. In a study by Bischoff *et al*, it was shown that EGEs are characterized by pronounced intestinal Eo accumulation and activation, whereas in IBD Eo are activated but their number is not or only slightly elevated compared to controls [54].

Our study highlights the fact that the presence of Eo and persistent lower gastrointestinal symptoms requires further monitoring and investigation, as in our cohort all such patients were later diagnosed with a type of colitis. Unlike in other studies with gastrointestinal eosinophilia, our cohort had a slight female predominance, with the mean age at diagnosis being the 5th decade of life.

Asthma has been reported in 32-39% of patients with eosinophilic esophagitis. [55,56]. It is known to coexist in patients with EGEs at similar rates [57-59]. In our cohort, patients with eosinophilia were more likely than the general population to have allergic rhinitis. However, there was no statistical significance when asthma and eczema were compared. Although such associations have been reported, our study group was small and further studies are warranted to evaluate this possible association. Allergic rhinitis usually precedes symptoms of eosinophilic esophagitis, suggesting that the initial sensitization might take place in the airways and that eosinophilic esophagitis is an extension of a preexisting IgE-mediated allergic syndrome [59].

Our study is one of the few available conducted on patients with initial gastrointestinal eosinophilia. This enabled us to follow up patients to assess symptom persistence or resolution. In fact, the diagnosis of IBD on repeat endoscopy is an aspect that has never been studied. Despite the fact that this study only included 66 patients, considering the lack of available literature it still highlights an important topic.

Limitations of this study include the absence of a control group without EGEs, and the fact that fecal calprotectin was not assessed and might have been higher in patients eventually diagnosed with IBD. However, we initially decided not to include it as this protein is not released by Eo and is therefore not useful in detecting the presence of EGEs. It is neutrophil-dependent and its levels might have been more prominent in patients eventually diagnosed with IBD.

In conclusion, we demonstrated that EGEs can precede the occurrence of IBD. Patients persistently symptomatic or who do not respond to treatment should be reassessed to exclude IBD, given its high prevalence in this group of patients.

Summary Box

What is already known:

- Eosinophilic esophagitis and gastroenteritis are chronic inflammatory conditions that can occur in response to allergens
- Eosinophilic esophagitis is defined as ≥15 eosinophils (Eo)/high power field (HPF), whereas eosinophilic gastrointestinal disorder in the rest of the gastrointestinal tract is usually defined as an eosinophilic count that exceeds 20 Eo/HPF
- Patients can present with dysphagia and a variety of non-specific gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea

What the new findings are:

- Asthma, allergic rhinitis and eczema can coexist in patients with eosinophilic gastrointestinal disorders
- Inflammatory bowel disease can be preceded by eosinophilic gastrointestinal disorders
- Patients with persistent symptoms and no explanation for the raised Eo on histology in the gastrointestinal tract should undergo repeat endoscopy

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