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Eosinophilic colitis: experience in a large tertiary hospital

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Abstract

Background: Eosinophilic colitis (EC) is a rare and ill-defined entity with an unknown pathogenesis and an unsatisfactory treatment response. The standard histopathological criteria for EC diagnosis lack specificity and not all the cases fulfilling those criteria are considered clinically as EC and treated. The objective of this study is to refine diagnostic criteria for EC. *Methods*: Retrospective study of all the cases with a histopathological diagnosis of EC in Hospital Clínico San Carlos (Madrid, Spain) from 2006 to 2016. We have reviewed their clinical and pathological features and tried to define the features differentiating cases considered EC on clinical grounds. *Results*: We identified 106 EC cases. In 22 cases, a clinical EC diagnosis was established. Confirmed EC was associated with younger age, female gender, diarrhea, higher maximum number of eosinophils/HPF (high-power field), intraepithelial eosinophils, architectural distortion and absence of acute inflammation. We chose a cut-off point of 40 for both mean and maximum number of eosinophils/HPF. A mean number of eosinophils/HPF higher than 40 was related to architectural distortion, mucosal atrophy, signs of eosinophil activation and submucosal infiltration. Cases with a maximum number of eosinophils/HPF higher than 40 showed more architectural distortion, intraepithelial eosinophils, submucosal infiltration and lack of lymphoplasmacytic infiltration. *Conclusions*: Histopathological diagnosis of EC is not well correlated with clinical EC. An increase in specificity can be achieved by raising the cut-off point to 40 eosinophils/HPF and by combining mean and maximum number of eosinophils with other microscopic and clinical features suggestive of EC.

Keywords: eosinophilic, colitis, eosinophil, large, bowel.

Introduction

Eosinophils are inflammatory cells with beneficial and adverse effects. They exert antiparasitic, antiviral and antibacterial effects and are involved in innate and adaptive immune responses [1]. Besides, they play a major role in certain pathologies, such as asthma, eczema, vasculitis or hypereosinophilic syndrome [2, 3]. Some authors have demonstrated a dysfunction of the epithelial barrier and an increase in fibroblastic proliferation and collagen production mediated by eosinophils in the gastrointestinal (GI) tract, both in culture models and GI disorders [3, 4].

Eosinophils are normally present in the GI tract, with the exception of the esophagus. They are found in the lamina propria, and their occurrence in this location is regulated by cytokines and chemokines, such as interleukin-3 (IL-3), IL-5 or eotaxin-3. These molecules also modify eosinophil survival, degranulation and development in the bone marrow [5–7].

In the normal large bowel, there is a non-pathological inflammatory infiltrate comprised of lymphocytes, plasma cells, eosinophils (3% of all inflammatory cells) and a small number of macrophages and mast cells [8]. It is known that there is a gradient in the number of eosinophils in the large intestine: they are supposed to decrease from proximal to distal regions [9]. However, there is no consensus about their normal range. In fact, authors have reported numbers ranging from 10–70 eosinophils per high-power field (HPF) in cecum to 1–30 eosinophils (HPF) in rectum [10].

Eosinophilic GI diseases have an increasing prevalence and are subdivided in eosinophilic esophagitis (EE), gastritis, colitis (EC) or gastroenteritis, depending on the region of the GI tract involved [7, 11]. EE is the best known of these diseases, with an established cut-off point of 15 eosinophils/HPF and other diagnostic criteria like the presence of microabscesses or the alteration of eosinophil mucosal distribution [12]. In respect of the large intestine, allergic proctocolitis and food-protein induced enterocolitis syndrome have been recognized in infants and children [13]. However, EC in adults is a rare and ill-defined condition with an unknown pathogenesis and an unsatisfactory treatment response [11]. The standard histopathological criteria for EC diagnosis lack specificity and not all the cases fulfilling those criteria are considered clinically as EC and treated. The objective of this study is to refine diagnostic criteria for EC.

Patients, Materials and Methods

This is a retrospective clinically-based study of the cases with histopathological diagnosis of EC in a large tertiary hospital (Hospital Clínico San Carlos) in Madrid, Spain. We have included all the cases histopathologically diagnosed of EC between 2006–2016. In this time period, a total of 106 large bowel biopsies were reported as large intestine mucosa with EC following the standard criterion of more than 20 eosinophils/HPF as stated in the literature. Specimens were formalin-fixed and paraffin-embedded, sectioned to 5-µm thickness and stained with Hematoxylin and Eosin (HE). Neither histochemical nor immunohistochemical techniques were performed. These cases were retrospectively reviewed by two independent pathologists to confirm diagnosis. Microscopic findings, such as number of total fragments per biopsy, number of involved fragments

per biopsy, mean eosinophil count per HPF, maximum eosinophil count per HPF, location and distribution of eosinophils, signs of eosinophil activation (eosinophilic abscesses, intraepithelial eosinophils, extensive degranulation), architectural distortion, mucosal atrophy, fibrosis, loss of epithelial mucin, presence of acute inflammation (cryptitis and/or microabscesses), lymphoplasmacytic infiltration and lymphoid follicular hyperplasia were assessed.

Mean number of eosinophils per HPF was calculated by counting eosinophils in five HPF in hot spots with the highest number of eosinophils. Maximum number of eosinophils per HPF was obtained from the HPF which contained the highest number of eosinophils. With this aim, we have used a Leica microscope with a field area of 0.18 mm^2 per HPF.

Medical records were also reviewed and demographic and endoscopic data were collected for the study, including age, gender, inflammatory bowel disease (IBD) diagnosis, food allergies, history of eosinophil-related diseases (asthma, dermatitis, scleroderma, dermatomyositis, polymyositis, hypereosinophilic syndrome), other GI disorders, regular medication (eosinophil-related drugs, such as chronic non-steroidal anti-inflammatory drugs (NSAIDs), clozapine, carbamazepine, tacrolimus, gold salts), diarrhea, severity of diarrhea (N1 diarrhea: 1–2 stools above normal per day; N2 diarrhea: 3–4 stools above normal per day; N3 diarrhea: five or more stools above normal per day), other clinical symptoms (rectal bleeding, weight loss, malabsorptive or obstructive symptoms, malnutrition, ascites) and presence of parasitic infections. Blood tests close in time to the biopsy sampling and endoscopic records were also reviewed, and we recorded the percentage of eosinophils in peripheral blood.

Although all the patients fulfilled histopathological criteria of EC in the biopsies, not all of them had been considered EC cases and treated accordingly on clinical grounds. With the aim of defining more specific histopathological criteria to define this entity, we have compared the histopathological features of these patients to those who were not considered clinical EC. The clinical and pathological features chosen for evaluation were extrapolated from the previous literature and they were also a consensual decision between the pathologists and clinicians involved in this study.

Statistical analysis

All the information has been analyzed with the SPSS 20.0 for Windows statistical package. For the analysis of association between variables, we have employed either χ^2 (chi)-squared test (qualitative variables) or Student's *t*-test (to compare means between dichotomic quantitative variables). For the aim of the present study, the statistical significance was settled at a *p*-value <0.05. The cut-off value for continuous quantitative variables has been established with a receiver operator curve (ROC) analysis. All the data have been obtained from the institutional electronic health record and database of Department of Surgical Pathology (PatWin).

Ethical considerations

The study was approved by the Ethical Committee of the Hospital, and the data have been stored and analyzed in an anonymized database to fulfill the requirements of the Spanish laws regarding personal data protection. Informed consent was not necessary due to the design of our study (anonymized retrospective case series).

Results

One hundred and six cases of patients with a histopathological diagnosis of EC were identified in the 10-year period of enrollment. Clinical features of all cases are summarized in Table 1.

Table 1 – ***Clinical features of patients with eosinophilic infiltration of the bowel wall (n=106)***

Age (mean, years)	50
Gender[a] (*n*, percent)	M: 46 (43.4%); F: 60 (56.6%)
Inflammatory bowel disease (IBD)[b] (*n*, percent)	10 (9.4%) UC: 7 (6.6%); CD: 3 (2.8%)
Food allergy (*n*, percent)	3 (2.8%)
Eosinophil-related diseases (*n*, percent)	9 (8.5%) Asthma: 7 (6.6%) Hypereosinophilic syndrome: 1 (0.94%) Kimura disease: 1 (0.94%)
GI disorders (*n*, percent)	Familial adenomatous polyposis (FAP): 7 (6.6%) Colonic adenocarcinoma: 6 (5.6%)
Drugs (*n*, percent)	3 (2.83%) Chronic use of NSAIDs: 2 (1.9%) Sulfasalazine: 1 (0.94%)
Diarrhea (*n*, percent)	70 (66%)
Rectal bleeding (*n*, percent)	12 (11.3%)
Other symptoms (*n*, percent)	Weight loss: 3 (2.8%) Obstructive symptoms: 1 (0.94%) Malabsorptive symptoms: 1 (0.94%)
Incidental finding (*n*, percent)	23 (21.7%)
Parasitic infection (*n*, percent)	7 (6.6%) *Anisakis*: 5 (4.71%) *Fasciola*: 1 (0.94%) *Strongyloides*: 1 (0.94%)
Peripheral blood eosinophilia (*n*, percent)	14 (13.2%)
Endoscopic findings (data available in 98 pts.) (*n*, percent)	No lesions: 71 (68.9%) Non-specific colitis: 15 (14.5%) IBD: 11 (10.6%) Compatible with EC: 1 (1%)

[a]M: Male, F: Female; [b]UC: Ulcerative colitis, CD: Crohn disease; NSAIDs: Non-steroidal anti-inflammatory drugs; IBD: Inflammatory bowel disease; EC: Eosinophilic colitis.

Mean age was 50 years and 60 (56.6%) patients were women. Ten (9.4%) patients had a previous diagnosis or were subsequently diagnosed as IBD. Only three (2.8%) patients referred food allergies. In regard of diseases associated with eosinophilia, seven (6.6%) patients had asthma, one patient (0.94%) had hypereosinophilic syndrome and one patient (0.94%) had Kimura disease. In two (1.9%) patients, a chronic use of NSAIDs was documented and one patient (0.94%) was taking mesalazine. In 23 (21.7%) cases, EC was an incidental finding, while 70 (66%) patients presented with diarrhea, the most common presenting symptom. Severity of diarrhea was recorded in 59 patients: nine patients had N1 diarrhea, 20 patients had N2, and 30 patients had N3 diarrhea. Other consulting symptoms found in our review were rectal bleeding (12 cases, 11.3%), weight loss (three cases, 2.8%), obstructive symptoms (one case, 0.94%) or malabsorptive symptoms (one case, 0.94%). Fourteen (13.2%) patients had peripheral blood eosinophilia (PBE), and in seven (6.6%) patients, a parasitic infection was detected. Two patients were also diagnosed with EE and eosinophilic gastritis.

Endoscopic data were available in 103 (97.2%) patients. Endoscopic studies revealed a normal intestinal mucosa in 71 (68.9%) patients, non-specific colitis in 15 (14.56%) patients, IBD features in 11 (10.67%) patients and EC features in one case (0.97%).

Microscopic findings of the endoscopic biopsies are summarized in Table 2.

Table 2 – *Histological features of patients with eosinophilic infiltration of the bowel wall (n=106)

Total biopsy fragments[a] Involved fragments	4.96 (min.: 1, max.: 13) 3.26
Mean number of eosinophils per HPF[b]	43.2 (min.: 7, max.: 199)
Maximum number of eosinophils per HPF	55.16 (min.: 10, max.: 253)
Level of infiltration in the bowel wall (*n*, percent)	Eosinophils mainly in lamina propria in all cases Homogeneous distribution: 59 (55.7%) Mainly superficial: 40 (37.7%) Submucosal infiltration: 7 (6.6%)
Architectural distortion (*n*, percent)	71 (66.98%)
Mucosal erosion (*n*, percent)	6 (5.7%)
Paneth cell metaplasia (*n*, percent)	6 (5.7%)
Mucosal atrophy (*n*, percent)	17 (16%)
Fibrosis (*n*, percent)	44 (41.5%)
Decrease of mucin (*n*, percent)	19 (17.9%)
Signs of eosinophil activation[c] (*n*, percent)	EA: 15 (14.2%) IE: 71 (67%) ED: 43 (40.6%)
Acute inflammation (*n*, percent)	17 (16%)
Lymphoid follicular hyperplasia (*n*, percent)	25 (23.6%)
Lymphoplasmacytic infiltration (*n*, percent)	28 (26.4%)

[a]min.: Minimum, max.: Maximum; [b]HPF: High-power field; [c]EA: Eosinophilic abscesses, IE: Intraepithelial eosinophils, ED: Extensive degranulation. *All quantitative variables are expressed as mean.

The number of fragments per biopsy ranged from one to 13 (mean: 4.96), and a mean of 3.26 of them were involved. Eosinophils were infiltrating the lamina propria in all cases, with a homogeneous distribution in 59 (55.7%) cases, superficial mucosal involvement in 40 (37.7%) cases and submucosal infiltration in seven (6.6%) cases. However, assessment of submucosal infiltration was not reliable, because most endoscopic biopsies did not include the submucosa. For this reason, muscularis propria or serosal involvement could not be assessed. Mean number of eosinophils per HPF ranged from seven to 199 (mean: 43.2), and maximum number of eosinophils per HPF ranged from 20 to 253 (mean: 55.16). The most frequent microscopic findings were architectural distortion (71 cases, 66.98%), intraepithelial eosinophils (71 cases, 66.98%), extensive eosinophil degranulation (43 cases, 40.6%) and fibrosis (44 cases, 41.5%) (Figures 1–3). None of our cases fulfilled criteria of microscopic colitis (either lymphocytic or collagenous colitis).

Twenty-two of 103 (21.3%) patients were clinically considered EC, and 18 (81.8%) of these patients were treated. Pharmacological treatment was prescribed in 12 (54.5%) patients: corticosteroids in five cases, budesonide in four cases, mesalazine in two cases and colchicine in one case. In three (13.63%) patients, dietary modifications were prescribed, and in three (13.63%) patients, combined dietary and pharmacological treatment was recommended. Treatment response was recorded in 15 (68.1%) patients, with a treatment response rate of 86.6% (13 patients). The remaining patients were not considered clinically suggestive of EC despite histopathological findings and none of them were treated. All have been followed-up on the long term, with no recurrence of symptoms.

We have compared EC and non-EC patients and results are summarized in Table 3.

Statistical analysis showed that EC patients were significantly younger (p=0.042, mean: 22 years) than non-EC patients (mean: 84 years). We also observed a trend towards significance for the association between EC and female gender (p=0.087), and presence of diarrhea (p=0.058). EC was more often associated with peripheral blood eosinophilia (p=0.024). Endoscopic findings showed no statistically significant differences between groups. With regard to microscopic findings, maximum number of eosinophils per HPF was higher in EC patients (mean: 73) than in non-EC patients (mean: 50), although this difference did not reach statistical significance (p=0.072). Mean number of eosinophils per HPF did not show statistically significant differences between groups, although it was higher in EC patients (55.8 *vs.* 39.9, p=0.116). We observed a trend towards significance for the association between EC and presence of intraepithelial eosinophils (p=0.096) and absence of acute inflammation (p=0.99) and architectural distortion (p=0.072).

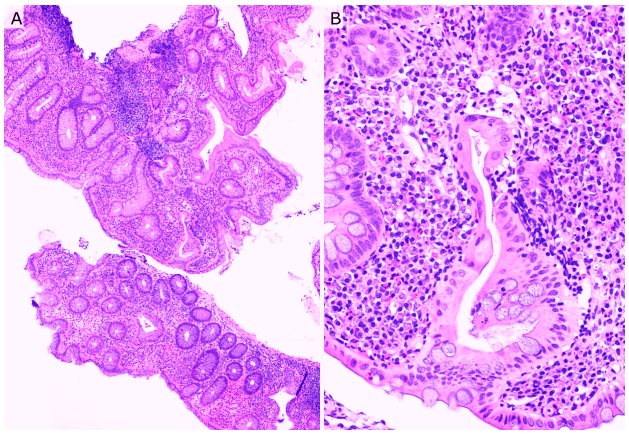

Figure 1 – *(A) Colonic mucosa showing architectural distortion; (B) Crypt distortion with loss of epithelial mucin. HE staining: ×100 (A); ×200 (B).*

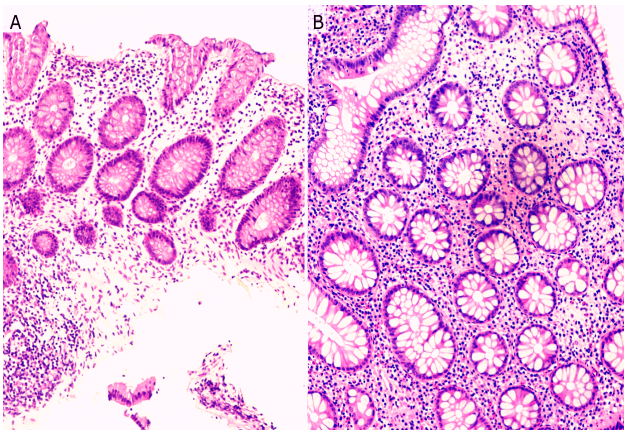

Figure 2 – *(A) Mucosal atrophy: Mild reduction in the number of crypts; (B) Fibrosis of the lamina propria. HE staining, ×100 (A and B).*

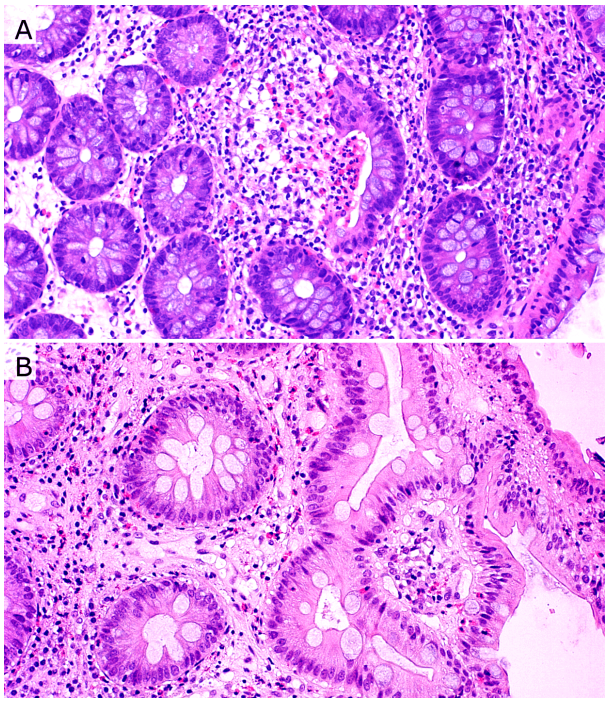

Figure 3 – ***(A) Eosinophil activation: Eosinophilic microabscess; (B) Eosinophil activation: Infiltration of the surface epithelium and crypts by eosinophils. HE staining, ×200 (A and B).***

Table 3 – ***Summary of the differences between clinically confirmed EC patients (n=22) and non-EC patients (n=84)****

Feature	Values in both groups	*P* value for the association
Age (years)[a]	EC: 22, NEC: 84	0.042
Maximum number of eosinophils per HPF[b]	EC: 73, NEC: 50	0.072
Mean number of eosinophils per HPF	EC: 55.8, NEC: 39.9	0.09
Females (percent)	EC: 72%, NEC: 52%	0.087
Diarrhea (percent)	EC: 86.3%, NEC: 63%	0.058
Peripheral blood eosinophilia (percent)	EC: 27%, NEC: 9.5%	0.024
Architectural distortion (percent)	EC: 14.2%, NEC: 33.3%	0.072
Intraepithelial eosinophils (percent)	EC: 81.8%, NEC: 63%	0.096
Acute inflammation (percent)	EC: 44.5%, NEC: 19%	0.09

[a]EC: Eosinophilic colitis patients, NEC: Non-eosinophilic colitis patients; [b]HPF: High-power field. All quantitative variables are expressed as mean. *We have included both significant differences (p<0.05) and trend to significance (p<0.1).

We chose a cut-off point of 40 eosinophils per HPF in the ROC curve for both mean and maximum number of eosinophils per HPF and we subsequently subdivided EC group into cases with ≤40 eosinophils/HPF and cases with >40 eosinophils/HPF. Results of the comparison between groups are summarized in Tables 4 and 5.

The presence of a mean number of >40 eosinophils/HPF was associated with architectural distortion (p=0.032), submucosal infiltration (p=0.007), and presence of acute inflammation (p=0.027). Cases with a mean number of >40 eosinophils/HPF showed more often mucosal atrophy, intraepithelial eosinophils, eosinophilic microabscesses and extensive eosinophil degranulation. Lymphoid follicular hyperplasia was detected more frequently in cases with a mean number of ≤40 eosinophils per HPF.

Cases with a maximum number of ≤40 eosinophils/HPF were more often associated with the presence of lymphoplasmacytic infiltration (p=0.027). A trend towards significance was seen in the association between cases with a maximum number of >40 eosinophils/HPF and level of eosinophilic infiltration in the bowel wall, architectural distortion or intraepithelial eosinophils.

Table 4 – ***Patients with clinically confirmed eosinophilic colitis: statistical differences between groups after establishing a cut-off value for the mean number of eosinophils/HPF of 40****

Feature	Values in both groups	*P* value for the association
Architectural distortion[a] (percent)	A: 41.8%, B: 22%	0.032
Level of infiltration in the bowel wall	All cases with submucosal infiltration were group A cases	0.007
Acute inflammation (percent)	A: 25.58%, B: 9.5%	0.027
Mucosal atrophy (percent)	A: 23.2%, B: 11.1%	0.094
Intraepithelial eosinophils (percent)	A: 76.7%, B: 60.3%	0.077
Eosinophilic microabscesses (percent)	A: 20.9%, B: 9.5%	0.098
Extensive degranulation (percent)	A: 51.56%, B: 33.3%	0.066
Lymphoid follicular hyperplasia (percent)	A: 16.3%, B: 31.7%	0.073

[a]A: Cases with more than 40 eosinophils/HPF, B: Cases with 40 or less eosinophils/HPF; HPF: High-power field. *We have included both significant differences (p<0.05) and trend to significance (p<0.1).

Table 5 – ***Patients with clinically confirmed eosinophilic colitis: statistical differences between groups after establishing a cut-off value for the maximum number of eosinophils/HPF of 40****

Feature	Values in both groups	*P* value for the association
Lymphoplasmacytic infiltration[a] (percent)	A: 18.75%, B: 38%	0.027
Level of infiltration in the bowel wall	All cases with submucosal infiltration were group A cases	0.089
Architectural distortion (percent)	A: 36%, B: 21%	0.1
Intraepithelial eosinophils (percent)	A: 73.4%, B: 57%	0.081

[a]A: Cases with more than 40 eosinophils/HPF, B: Cases with 40 or less eosinophils/HPF; HPF: High-power field. *We have included both significant differences (p<0.05) and trend to significance (p<0.1).

Discussion

Some authors suggest that food allergens may play a key role in the pathogenesis of EE. History of atopy is documented in 50–90% of cases and food antigens are the most frequently detected cause of EE [14, 15]. Thus, EE is supposed to be an atopic disorder mediated by type 2 T-helper lymphocytes (Th2) [11]. EC is, nonetheless, a deficiently studied disease and its pathogenesis is unknown. Most cases in infancy are related to food allergens, causing allergic proctocolitis. Th2 is thought

to play a key role in the development of adult cases too, but the possible triggering factors have not been identified [16, 17]. In general, many disorders have been related to GI eosinophilia, including food allergy, asthma, dermatitis, scleroderma, dermatomyositis, polymyositis, hypereosinophilic syndrome, parasitic infections or drug-induced colitis. EC has also been shown to be more frequent in atopic patients [8]. In our study, only three patients with clinically diagnosed EC were asthmatic and none of them had a history of food allergy. Thus, we have not been able to confirm this alleged statistically significant association between EC and food allergy or diseases associated with eosinophilia.

EC has a bimodal age distribution. It occurs mainly in infants and young adults, although cases in older patients have been reported [18]. This predilection for the younger group has also been confirmed in the present study. We have found a trend towards signification between the association between female gender and EC, but previous studies have shown no gender predilection [8].

The signs and symptoms of EC vary depending on the large bowel region involved by the disease and the depth of bowel wall involvement. Klein *et al.* subdivided eosinophilic gastroenteritis into three main subtypes: mucosal, transmural and serosal EC (in descending order of frequency) [19]. In mucosal EC, eosinophils are located in the superficial aspect of the mucosa and the patients present with malabsorption, protein loss and diarrhea [20]. If the infiltrate involves the muscularis propria the clinical symptoms are bowel obstruction, volvulation, intussusception and thickening of the bowel wall. An intestinal perforation may occur [21]. Serosal EC presents with ascites and a marked increase of eosinophils in the abdominal fluid. Most of our patients presented with diarrhea, but we cannot correlate symptoms with depth of eosinophilic infiltration, for all our biopsies are endoscopic biopsies, and submucosa, muscularis propria and serosa are generally not sampled.

Complementary tests can be performed, but they have limitations due to their lack of sensitivity and specificity. First, allergic skin testing can exclude an immunoglobulin E (IgE)-mediated food allergy but a positive test does not confirm the diagnosis of EC [22]. Blood test may show anemia or low levels of albumin. In some cases, there is an increase of levels of erythrocyte sedimentation rate and C-reactive protein, which are signs of peripheral inflammation [23]. In respect of peripheral blood eosinophilia (PBE), we have found statistically significant differences between EC and non-EC patients. However, PBE was only present in 27% of EC patients and 57% of patients with PBE were not diagnosed with EC. Thus, this finding can be useful only in combination with other clinical and pathological information.

Endoscopic findings were suggestive of EC only in one patient. Previous studies have shown that many EC patients have no endoscopic alterations, and if present, they are usually not specific. The colonic mucosa may show patchy erythematous changes, loss of vascular pattern or mild superficial ulceration [22]. In this sense, we could regard EC as one of the so-called microscopic colitis, for patients most frequently consult on diarrhea (66%) and usually show no endoscopic abnormalities.

A biopsy should therefore be performed for diagnostic confirmation of EC and exclusion of other possible causes. However, endoscopic biopsies are not useful to assess the depth of eosinophilic infiltration, and multiple biopsies should be obtained due to the patchy distribution of the disease. Features commonly found in these biopsies are increased mucosal eosinophils, altered eosinophil distribution, extensive degranulation, eosinophilic abscesses, intraepithelial eosinophils, reactive epithelial changes or lack of acute inflammation [24]. Regarding the number of mucosal eosinophils, the cut-off point for diagnosing EC is not well settled. Most studies suggest a cut-off point of 20 eosinophils/HPF. Our study shows that this cut-off point does not precisely discriminate between EC and other diseases leading to tissue eosinophilia, for only 21.3% of the cases classified as EC on histopathological grounds were clinically suggestive of this diagnosis. Given that eosinophils are normally present in the bowel mucosa in non-pathological conditions, this minimum number of eosinophils is probably too low for the specific identification of EC cases. Some authors have suggested a minimum of 60 eosinophils/HPF [25] and Collins established different cut-off points for different large intestine areas (>100 eosinophils/HPF in the right colon, >84 eosinophils/HPF in transverse and descending colon and >64 eosinophils/HPF in sigmoid colon and rectum) [24].

In our study, we have not been able to perform this kind of analysis to define separate cut-off points, for most biopsies (specially from normal endoscopies) are taken together from different areas of the large intestine wall and submitted in only one container to the Department of Pathology. Nevertheless, this lack of proper location of the biopsies is common in everyday practice, so we feel our study is rather representative of real clinical situation and can be useful for practicing pathologist faced with this diagnosis. We have chosen a cut-off point of 40 eosinophils/HPF for both mean and maximum number of eosinophils per HPF. With this cut-off point, we can achieve a sensitivity of 60% and specificity of 50% for the diagnosis of EC (ROC analysis).

Thus, the number of eosinophils per HPF should be considered in combination with other microscopic features and clinical findings. Our results suggest that the microscopic findings most closely related to EC are the presence of architectural distortion, intraepithelial eosinophils and the absence of acute inflammation. Clinical findings, such as age and gender of patients, presence of diarrhea or peripheral blood eosinophilia can also support an EC diagnosis.

We recommend the elaboration of an EC protocol including the following items: mean eosinophil count per HPF, maximum eosinophil count per HPF, location and distribution of eosinophils, signs of eosinophil activation (eosinophilic abscesses, intraepithelial eosinophils and extensive degranulation), architectural distortion, mucosal atrophy, fibrosis, loss of epithelial mucin, presence of acute inflammation, lymphoplasmacytic infiltration and lymphoid follicular hyperplasia. Microscopic findings are separately reported, but they are not specific and should be considered together. Mueller highlighted that a non-specific increase in eosinophils is commonly found

in large bowel biopsies, without any obvious explanation [26].

The differential diagnosis should include all possible causes of intestinal eosinophilia. Some histological findings can be helpful, such as eosinophil distribution (eosinophilic infiltration is focal in collagenous and lymphocytic colitis), the presence of acute inflammation (which is more frequently associated to inflammatory bowel disease), the identification of parasite fragments in an edematous background, or the presence of epithelial cell vacuolization and apoptosis (features seen in drug-induced EC). Some authors suggest that eosinophilic infiltration of the bowel wall is associated with IBD relapses. However, our results do not support this hypothesis [23]. A final diagnosis can be rendered only after clinical correlation and exclusion of all other possibilities.

In respect of EC treatment, no randomized controlled trials have been performed, and all available data come from small series of cases or case reports. Clinical management can also be extrapolated from other eosinophilic GI diseases. There are several treatment options: corticosteroids, mast cell inhibitors or leukotriene receptor antagonists, azathioprine or 6-mercaptopurine, IL-5 inhibitors or dietary modifications. Several studies have demonstrated an improvement in symptoms control with corticosteroids, but without histological correlation [27, 28]. The usual dosage is similar to that of inflammatory bowel disease, and should be reduced gradually. Relapses are common and a maintenance therapy is usually necessary [29]. Mast cell inhibitors and leukotriene receptor antagonists have also demonstrated an improvement in symptoms control, and they are frequently used in combination with other drugs [30, 31]. Azathioprine and 6-mercaptopurine inhibit eosinophil growth factors and reduce the number of infiltrating eosinophils [32]. IL-5 inhibitors are still being studied and some authors suggest that they could be used in refractory or severe cases [7]. Allergic tests and dietary modifications have been useful in eosinophilic proctocolitis in children, but in adults response to treatment is variable [22]. There are three dietary options: an elemental diet, specific antigen avoidance and empiric food elimination depending on the most common food antigens [11]. In EE, some studies showed that dietary treatment resolved 50–80% of cases [33]. However, Lucendo *et al.*, in their systematic review, concluded that the unequivocal use of dietary treatment for patients with primary eosinophilic GI disease cannot be supported [13].

As for the course of the disease, EC in infants and children has a good prognosis, and tends to resolve within several days. The food allergen can also be reintroduced in a few years [34]. However, in young adults EC is more frequently a chronic disease with symptomatic periods followed by periods of remission [22].

Conclusions

EC is a rare and not well-known disease. Large bowel biopsies diagnosed as intestinal wall with eosinophilic infiltration do not correspond to a unique specific entity. The most used cut-off point for diagnosing EC, 20 eosinophils per HPF, does not allow the recognition of EC cases due to its lack of specificity. Thus, most of biopsies diagnosed by pathologists as EC do not have clear clinical correlates. An increase in specificity can be achieved by raising the cut-off point to 40 eosinophils/HPF and by combining mean and maximum number of eosinophils with other microscopic and clinical features suggestive of EC, such as presence of architectural distortion, intraepithelial eosinophils, absence of acute inflammation, young age, female gender, presence of diarrhea or peripheral blood eosinophilia.

Conflict of interests

The authors declare that they have no conflict of interests.

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