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Recurrent blood eosinophilia in ulcerative colitis is associated with severe disease and primary sclerosing cholangitis

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Abstract

Background and Aims—Eosinophils are implicated in the pathogenesis of inflammatory bowel disease (IBD). A subset of IBD patients develops blood eosinophilia and the clinical profile of these patients is undefined. We sought to characterize IBD patients with and without eosinophilia.

Methods—We studied a prospective registry of 1176 IBD patients followed in a tertiary referral center. Patients who developed eosinophilia at any time were identified by electronic medical record query. We performed a chart review case-control study comparing patients with recurrent eosinophilia versus randomly selected disease matched patients with no history of eosinophilia. Histological analysis was performed on selected cases and controls.

Results—Eosinophilia at any time was more prevalent in ulcerative colitis (UC) patients than Crohn's disease patients (22.2% vs. 12.7%), as was recurrent eosinophilia (3.4% vs. 0.7%). UC patients with recurrent eosinophilia were predominantly male compared to the control UC population (81.3% vs. 46.9%) and had higher rates of colectomy for either medically refractory disease or dysplasia/cancer than control UC patients (56.3% vs. 15.6%). Primary sclerosing cholangitis (PSC) occurred in 37.5% of UC patients with recurrent eosinophilia compared to only 3.1% in the UC controls. Histological analysis of random diagnostic samples from UC patients with recurrent eosinophilia demonstrated a normal eosinophil pattern as seen in the control UC population.

Conclusions—Eosinophilia-associated UC is a subgroup of IBD associated with severe colitis and PSC. Further studies are warranted to characterize molecular mechanisms underlying eosinophilia-associated UC and to determine optimal approaches for therapy.

Keywords

eosinophils; inflammatory bowel disease; primary sclerosing cholangitis; ulcerative colitis

INTRODUCTION

Eosinophils are granulocytic leukocytes that play a key role in mucosal innate host defense, particularly against helminth infections [1]. Eosinophils promote inflammation via the release of toxic granule proteins and free radicals, as well as the production of multiple pro-inflammatory mediators such as prostaglandins, leukotrienes, and cytokines. Eosinophils also stimulate adaptive immune responses via antigen presentation and T cell recruitment. Accordingly, eosinophils have been implicated in the pathogenesis of asthma, eosinophilic esophagitis (EoE), and other chronic inflammatory mucosal disorders, including inflammatory bowel disease (IBD) [2-4].

Eosinophils are found in excess in IBD, where they are postulated to modulate both tissue injury and repair [5]. Eosinophils originate in the bone marrow and migrate predominantly to the gastrointestinal tract under the influence of interleukin-5 and the eotaxin chemokines, all of which are overexpressed in IBD [6,7]. Eosinophils normally comprise only a small proportion of circulating leukocytes. However, blood eosinophilia has been identified as a biomarker of EoE and of distinct asthma subtypes [8,9]. Blood eosinophilia has also been observed in select cases of IBD, particularly in ulcerative colitis (UC), for which it has been proposed that eosinophilia reflects a unique pathogenesis [10-12].

The clinical profile of IBD patients with blood eosinophilia has not been described with respect to treatment specific response, intestinal and extraintestinal complications, and outcomes. Since IBD encompasses a heterogeneous group of inflammatory disorders similar to asthma, we hypothesized that blood eosinophilia identifies a specific subset of IBD patients with distinctive clinical characteristics. Therefore, we sought to define the clinical profile of IBD patients with and without blood eosinophilia from a tertiary care center research registry.

METHODS

Selection of cases and controls

The study population consisted of patients with either Crohn's disease (CD) or ulcerative colitis (UC) who enrolled in the University of Pittsburgh Medical Center (UPMC) Inflammatory Bowel Disease Research Registry from 2000 to 2009. The research registry facilitates retrospective research studies on IBD, as registry participants provide written informed consent to allow analysis of their identifiable medical record information. Enrollment and participation in the research registry was approved by the University of Pittsburgh Institutional Review Board.

The study involved a search of the Medical Archival Retrieval System (MARS) at UPMC, a repository of electronic medical records (EMR). Using UPMC MARS, IBD registry patients were identified who had blood eosinophilia, defined by an absolute eosinophil count (AEC) greater than normal (upper limit of normal, $0.4 \times 10^9/\text{liter}$ (L), as defined by UPMC clinical laboratory), on a complete blood count at any time between 1996 and 2009. To focus our attention on individuals with likely eosinophilia-associated IBD, we sought to find subjects with significant and recurrent eosinophilia and defined cases as IBD patients who had AEC equal to or greater than $0.5 \times 10^9/\text{liter}$ (L) on at least 4 separate occasions, with at least 2 episodes occurring 4 or more weeks apart.

Based on an observed association between eosinophilia and UC, a case-control study of eosinophilia-associated UC (EoUC) was subsequently performed. Control subjects with UC and at least 2 or more clinic or hospital visits and at least 6 months of follow-up and no history of eosinophilia were randomly selected from the same registry population. Two UC

controls were selected for every one EoUC case. No matching strategy was utilized for the cases and controls, as we wanted to use an unbiased approach to better understand the characteristics of patients with UC and eosinophilia. No patients were censored from inclusion in this study, such as patients with a history of colectomy who subsequently enrolled into the research registry.

Chart review

In-depth phenotyping of cases and controls was performed by chart review of all available records in UPMC MARS through 2010 including progress notes, letters, discharge summaries, operative notes, imaging reports, endoscopy reports, and surgical pathology reports. Multiple characteristics were recorded for each case and control subject including age, gender, race, family history of IBD, tobacco history, allergies, extent of disease, surgical and hospitalization history, IBD medication history, extraintestinal manifestations, and other co-morbidities. In addition, the clinical scenarios associated with the development of eosinophilia were characterized including disease symptoms, medication changes, preceding surgeries, and concurrent infections.

Histological evaluation

Original diagnostic hematoxylin and eosin stained slides from biopsy and surgical material of the study population were analyzed for the presence of tissue eosinophils. Eosinophilia was assessed in three compartments in intestinal specimens – epithelium, lamina propria and muscularis mucosa. Liver specimens were evaluated for eosinophils within the biliary epithelium, portal tracts, and between hepatocytes.

Statistical analysis

Dichotomous data are expressed as total number and percentages and were compared using the Fisher's exact test or Chi-square test. Continuous data are expressed as medians (interquartile range) and were compared using the Mann-Whitney test. All tests were 2 sided, and *P* values less than 0.05 were considered statistically significant.

RESULTS

Prevalence of blood eosinophilia in IBD patients

There were 203 out of 1176 IBD registry patients who demonstrated elevated blood eosinophils at any time between 1996 and 2009 (17.3%). The distribution of eosinophilia among the IBD patients was not equal. Among the UC patients, there were 22.2% (104 out of 468 total UC patients) who demonstrated evidence of eosinophilia at any time, while only 12.7% CD patients (90 out of 708 total CD patients) had this finding ($p < 0.0001$; Chi-Square test).

Our next analysis focused on individuals who demonstrated significant and recurrent eosinophilia, defined by an AEC equal to or greater than $0.5 \times 10^9/L$ on at least 4 separate occasions, with at least 2 episodes occurring 4 or more weeks apart. We identified recurrent eosinophilia in 3.4% of UC patients (16 out of 468 total UC patients) and 0.7% of CD patients (5 out of 708 total CD patients), which was significantly more common in the UC cohort compared to CD ($p = 0.001$; Fisher's exact test). These 16 UC patients with recurrent eosinophilia were designated as having eosinophilia-associated UC (EoUC) and underwent in-depth phenotyping via chart review and 32 UC patients without any history of blood eosinophilia were randomly selected from the registry to serve as control subjects for a case-control study of EoUC.

Clinical characteristics of EoUC and control UC patients

We found that there was a significant male predominance in the EoUC cohort compared to the UC control population, while there was no difference in age, age at diagnosis, race, or smoking history between the two groups (Table 1).

EoUC patients tended to have a longer duration of disease and had a significantly greater extent of disease than control UC patients (Table 2). EoUC patients had a longer duration of follow-up than control UC patients. Although the duration of follow-up in the control group was shorter than the EoUC cohort, the median duration of follow-up of control UC patients was still 4.2 years, with 87.5% of control UC patients followed for at least 2 years.

EoUC patients had a more severe disease course as characterized by history of IBD-related hospitalizations, colectomy for a complication or treatment of UC, and steroid therapy. Colectomy was required for medically refractory disease in 43.8% of EoUC patients and for dysplasia or cancer in 12.5% of EoUC patients. Colectomy was required for medically refractory disease for only 12.5% of control UC patients and for dysplasia or cancer for only 3.1% of control UC patients. We also evaluated the patterns of medical therapy that were used in the EoUC and control UC cohorts. We found that patterns of biologic therapy (i.e. infliximab) and immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) were similar in the EoUC and control UC cohorts.

Next we evaluated the rates of extraintestinal manifestations of IBD in UC patients with and without recurrent eosinophilia. EoUC and control UC patients had similar low rates of extraintestinal manifestations of IBD such as joint, skin, or eye disease (data not shown). In contrast, EoUC patients had a much higher likelihood of primary sclerosing cholangitis (PSC) than control UC patients (37.5% vs. 3.1%, $p=0.004$; Fisher's exact test). One of the EoUC-PSC patients had overlap autoimmune hepatitis (AIH), while another EoUC patient developed distinct AIH in the absence of PSC. There was no history of AIH in the control UC cohort. Three out of the 6 EoUC-PSC patients and the one EoUC-AIH patient required liver transplantation, including one EoUC-PSC patient who required a second liver transplant for recurrent PSC. Another EoUC-PSC patient developed de novo AIH after liver transplantation. The one control UC-PSC patient also required liver transplantation.

Chronic colonic inflammation is associated with the development of dysplasia and cancer in IBD and we evaluated rates of this neoplastic complication in UC patients with and without eosinophilia. 12.5% of EoUC patients developed colon dysplasia or cancer compared to 6.3% of control UC patients. PSC is associated with higher rates of colon dysplasia/cancer, but only 1 of the 6 EoUC-PSC patients developed colon dysplasia or cancer and the one control UC-PSC patient had no history of colon dysplasia or cancer.

None of the EoUC patients were diagnosed with systemic mastocytosis or hypereosinophilic syndrome (defined by persistent blood eosinophilia $1.5 \times 10^9/L$, absence of a secondary cause, and a primary eosinophilic disease), and there were no cases of EoE or other primary eosinophilic gastrointestinal disorders in either group. None of the EoUC patients had a history of asthma, while 3 of the control UC patients had reported asthma. EoUC and control UC patients had an equal predisposition for drug allergies. In contrast, EoUC patients had a higher reported history of infections, including, 3 cases of *Clostridium difficile*, 1 case of CMV, 2 cases of bacterial pneumonia, 1 case of line infection, and 3 cases of intraabdominal abscesses, but no documented parasitic infections. In the control UC cohort, there were 1 reported case of *Clostridium difficile*, 1 case of pneumonia, 1 case of CMV, and 1 case of oral candidiasis.

Clinical scenarios associated with eosinophilia in EoUC patients

To differentiate between disease related episodes of eosinophilia versus possible confounding agents, we characterized the clinical scenarios associated with 69 distinct episodes of eosinophilia in the 16 EoUC patients, with episodes in the same patient separated by at least a 4 week interval (Table 3). We found that 13.0% of the eosinophilia episodes (9 eosinophilia episodes in 5 EoUC patients) occurred during a known UC flare, including 4 episodes in one particular patient. 17.4% of the eosinophilia episodes (12 episodes of eosinophilia in 3 EoUC patients) occurred in patients with active PSC. 21.7% of the eosinophilia episodes (15 episodes of eosinophilia in 11 EoUC patients) occurred in the post-operative setting after colectomy, ileostomy takedown or liver transplantation. Only 1.4% of eosinophilia episodes occurred during an apparent drug reaction and 5.8% of eosinophilia events occurred during a known infection, none of which were parasitic. Thirteen EoUC patients had distinct episodes associated with different known clinical scenarios (i.e. UC or PSC flare, surgery, etc.). The remaining clinical scenarios associated with eosinophilia were unknown because of either deficient medical records and/or absence of any concurrent clinical signs or symptoms.

Histological evaluation

We sought to determine the extent of intestinal eosinophils in the EoUC cohort by analyzing a random assortment of original diagnostic specimens from 88% of the EoUC patients. Overall, we found no specific increase or distribution of intestinal eosinophils in the analyzed EoUC specimens compared to the control UC population. Sixty percent of the examined EoUC cases showed eosinophils within the epithelium (greater than 1/100 enterocytes) with the highest amount reaching 20 eosinophils per 100 enterocytes. The cases demonstrating the most severe epithelium infiltration of eosinophils demonstrated only mildly active colitis. The eosinophils within the epithelium were histologically distinct from Paneth cells. All of the cases showed eosinophils within the lamina propria ranging from 20% (13 eosinophils per high power field) of the lamina propria inflammatory cells to 70% (110 eosinophils per high power field). Twenty percent of the examined cases showed more than single cells within the muscularis mucosa (ranging from 3 to 20 eosinophils per high power field). No relationship was identified between the activity level of the colitis and the percent of eosinophils within the lamina propria or the presence of eosinophils within the muscularis mucosa. Surgically resected specimens from two EoUC patients showed eosinophils within the muscularis propria (4 to 6 eosinophils per high power field). No histologic evidence of mast cells or Charcot-Leyden crystals was identified in any of the specimens.

Liver specimens from the 7 EoUC-PSC patients were also examined for eosinophils. Two of the seven cases showed rare eosinophils within the biliary epithelium. One case did not show eosinophils within the portal tracts, while the other cases showed rare (1 to 2 eosinophils per high power field) to occasional eosinophils (5 to 20 eosinophils per high power field). Four out of seven cases showed no eosinophils between hepatocytes, while three cases showed single to few eosinophils between hepatocytes. Six out of seven cases had active inflammation, and the amount of neutrophils within the bile duct did not correlate with the few cases with increased tissue eosinophils. Finally, we observed no correlation in the tissue eosinophil pattern in five out of the seven patients who had available intestinal biopsies as well as liver specimens.

DISCUSSION

In this study we evaluated blood eosinophilia in a large cohort of IBD patients and found that eosinophilia was frequently encountered, occurring in 17% of individuals at any time

during the course of their illness. Transient and recurrent eosinophilia was more common in UC compared to CD. More focused analysis of UC patients with recurrent blood eosinophilia compared to UC without eosinophilia revealed: 1) male predominance; 2) more severe disease; and 3) predisposition for PSC. These findings are consistent with prior studies demonstrating an association between eosinophils and UC, and provide novel information suggesting that recurrent blood eosinophilia in UC may function as a biomarker for a phenotype of patients with more complicated intestinal and extraintestinal disease.

UC is considered a secondary eosinophilic gastrointestinal disorder, as blood and tissue eosinophilia is a feature of many cases [1]. In accordance with eosinophil biology, UC has been proposed to be caused by allergic-mediated inflammation. Unlike CD, UC is promoted by CD4⁺ T helper 2 (Th2) cells [13], which modulate atopic disease by producing cytokines that stimulate B cells and promote allergic responses. Consequently, UC lesions are characterized by a significant number of plasma cells, and UC patients have greater than normal levels of circulating and tissue IgG antibodies[14].

Early prospective studies of UC demonstrated that approximately one-third of patients with UC have an increase in blood eosinophils during active or relapsing disease [11,12]. It was postulated that UC may be an allergic disorder in these individuals with eosinophilia given the frequent association with eosinophils and allergic disease. Subsequent studies performed in the United Kingdom found that eosinophilia more often occurs in UC patients of Asian descent than in white Caucasians, suggestive of alternative pathogenesis of UC [10]. None of the Asian UC patients demonstrated evidence of intestinal parasites, suggesting that the eosinophilia was an intrinsic immune mechanism in their disease. Our study demonstrates that eosinophilia is also a feature of a distinct cohort of Caucasian UC patients, particularly UC patients with PSC.

PSC is a rare and irreversible cause of liver failure, which is characterized by progressive inflammatory destruction of the bile ducts [15]. PSC most often occurs in patients with concomitant IBD, especially in patients with pan UC, as was the case for all 6 EoUC-PSC patients identified in our study. Accordingly, PSC is considered an extraintestinal manifestation of UC. Consistent with our findings, blood eosinophilia has been described in numerous cases of PSC, including, at the initial presentation of disease [16,17]. Similar to UC, eosinophilia is more common in Asian PSC patients than PSC patients from Western countries [18]. Asian PSC patients also have a higher incidence of anti-nuclear antibodies and case reports have described higher levels of serum IgE, indicative of different disease mechanisms for PSC.

Like the EoUC cohort, PSC predominantly affects males. Male preponderance is also a characteristic of EoE [19]. The common association between male preponderance and PSC, EoE, and the EoUC cohort suggests that males are predisposed to eosinophilic-mediated digestive diseases. Fibrosis is another common feature of chronic UC, PSC and EoE, which has been shown to be promoted by eosinophil-derived transforming growth factor beta (TGF- β) and eosinophil granule major basic protein, thereby linking eosinophils to disease pathogenesis [3]. Relevant to the chronic inflammatory changes in the colon, UC and PSC are significant risk factors for dysplasia and colon cancer, which were increased in the EoUC cohort compared to the control UC group.

UC patients have a greater likelihood of having asthma than the normal population, but otherwise there is no clear link between UC and atopic disease in contrast to EoE [20,21]. Despite eosinophilia and its association with allergic disease, we did not find a higher frequency of drug allergies or major atopic disease, such as asthma, in the EoUC cohort compared to control UC cohort. Nor did we identify any IBD patients with EoE,

hypereosinophilic syndrome, or systemic mastocytosis. We did not determine the prevalence of other atopic diseases such as food allergies, allergic rhinitis or eczema due to the limited medical record information. Thus, the overall burden of atopic disease in our study cannot be accurately concluded.

The major limitations of our study were the small sample size and the retrospective design of the data acquisition from chart review. Thus, the possibility of selection bias, information bias, and confounding exists in our study. Selection bias is a concern for our study since the EoUC cohort consisted of more hospitalized patients than the control UC cohort, and consequently EoUC patients had more blood cell counts on average than control UC patients due to differences in level of care. EoUC patients also had a longer duration of follow-up than control UC patients, which further predisposes selection bias. Information bias is another issue in our study, as we were unable to fully characterize the clinical scenarios of all eosinophilic episodes because of incomplete medical records.

To eliminate possible confounders such as drug reactions, parasitic infections, food allergies, and malignancy, we included in our analysis only UC patients who had recurrent eosinophilia. Via this approach, we found that a significant number of eosinophilic episodes were concurrent with active UC or PSC with no other obvious inciting agent such as a new medication, as 31.3% of EoUC patients had blood eosinophilia during known UC flares, which is similar to previous reports that identified eosinophilia in approximately one-third of UC patients [11,12]. However, we observed that a greater number of eosinophilic episodes occurred immediately after bowel surgery or liver transplantation, suggestive of a possible confounder such as anesthesia or the surgical intervention itself.

Post-operative elevations in plasma cortisol after colectomy should theoretically suppress blood eosinophilia [22]. Accordingly, blood eosinophilia has never been reported after colectomy or ileostomy takedown for any indication, including IBD, colorectal cancer and familial adenomatous polyposis. However, blood eosinophilia has been occasionally observed after liver transplantation and has been identified as an early marker of organ rejection [23-25]. Consistent with this observation, 1 EoUC-PSC developed blood eosinophilia concurrent with known acute hepatic allograft rejection. Thus, post-operative eosinophilia may represent an abnormal immune response in predisposed individuals such as in the EoUC cohort. The apparent increased risk of infection in EoUC patients may also indicate an attenuated immune reaction against pathogens.

Finally, as this was a retrospective study, we were unable to correlate circulating eosinophilia with tissue eosinophilia in the EoUC patients. However, we attempted to assess the extent of intestinal and liver eosinophils in the EoUC cohort by analyzing a random assortment of original diagnostic specimens. In general, we found that there was no specific increase or distribution of tissue eosinophils in the EoUC patients compared to the control UC population, and that the number of eosinophils in the examined intestinal specimens are likely within the normal site-specific range of colonic mucosal eosinophils [26]. Our observations are consistent with earlier prospective studies that demonstrated a rather poor correlation between circulating and tissue eosinophils [12]. These findings suggest that blood eosinophilia is an extraintestinal manifestation of UC independent of bowel disease.

In conclusion, we identified a rare cohort of UC patients with recurrent blood eosinophilia, which correlated with severe disease and a high likelihood of PSC. UC patients with eosinophilia may have a unique immunopathogenic basis for their disease, which underlies refractory chronic inflammation associated with tissue destruction and fibrosis. Thus, prospective studies are warranted to further characterize the natural history and disease mechanisms of EoUC patients in order to determine optimal approaches of therapy.

Additional studies are warranted to investigate the clinical profile of PSC patients with and without blood eosinophilia.

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References

1. Powell N, Walker MM, Talley NJ. Gastrointestinal eosinophils in health, disease and functional disorders. *Nat Rev Gastroenterol Hepatol*. 2010; 7:146–156. [PubMed: 20125092]
2. Wenzel SE. Eosinophils in asthma--closing the loop or opening the door? *N Engl J Med*. 2009; 360:1026–1028. [PubMed: 19264692]
3. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. *Gastroenterology*. 2009; 137:1238–1249. [PubMed: 19596009]
4. Woodruff SA, Masterson JC, Fillon S, Robinson ZD, Furuta GT. Role of eosinophils in inflammatory bowel and gastrointestinal diseases. *J Pediatr Gastroenterol Nutr*. 2011; 52:650–661. [PubMed: 21593640]
5. Al-Haddad S, Riddell RH. The role of eosinophils in inflammatory bowel disease. *Gut*. 2005; 54:1674–1675. [PubMed: 16284283]
6. Lampinen M, Carlson M, Sangfelt P, Taha Y, Thorn M, Loof L, Raab Y, Venge P. Il-5 and tnf-alpha participate in recruitment of eosinophils to intestinal mucosa in ulcerative colitis. *Dig Dis Sci*. 2001; 46:2004–2009. [PubMed: 11575456]
7. Mir A, Minguez M, Tatay J, Pascual I, Pena A, Sanchiz V, Almela P, Mora F, Benages A. Elevated serum eotaxin levels in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2002; 97:1452–1457. [PubMed: 12094864]
8. Konikoff MR, Blanchard C, Kirby C, Buckmeier BK, Cohen MB, Heubi JE, Putnam PE, Rothenberg ME. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2006; 4:1328–1336. [PubMed: 17059896]
9. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF Jr, Wardlaw AJ, Wenzel SE, Greenberger PA. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011; 127:355–360. [PubMed: 21281866]
10. Benfield GF, Asquith P. Blood eosinophilia and ulcerative colitis--influence of ethnic origin. *Postgrad Med J*. 1986; 62:1101–1105. [PubMed: 3658847]
11. Riis P, Anthonisen P. Eosinophilia in peripheral blood and inflammatory exudate in non-specific proctocolitis. *Acta Med Scand*. 1964; 175:85–89. [PubMed: 14110641]
12. Wright R, Truelove SC. Circulating and tissue eosinophils in ulcerative colitis. *Am J Dig Dis*. 1966; 11:831–846. [PubMed: 5953694]
13. Strober W, Fuss JJ. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. *Gastroenterology*. 2011; 140:1756–1767. [PubMed: 21530742]
14. Kett K, Rognum TO, Brandtzaeg P. Mucosal subclass distribution of immunoglobulin g-producing cells is different in ulcerative colitis and crohn's disease of the colon. *Gastroenterology*. 1987; 93:919–924. [PubMed: 3308623]
15. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010; 51:660–678. [PubMed: 20101749]
16. Horiuchi K, Kakizaki S, Kosone T, Ichikawa T, Sato K, Takagi H, Mori M, Sakurai S, Fukusato T. Marked eosinophilia as the first manifestation of sclerosing cholangitis. *Intern Med*. 2009; 48:1377–1382. [PubMed: 19687582]

17. Shimomura I, Takase Y, Matsumoto S, Kuyama J, Nakajima T, Maeda H, Sugase T, Hata A, Hanada M, Okuno M. Primary sclerosing cholangitis associated with increased peripheral eosinophils and serum ige. *J Gastroenterol.* 1996; 31:737–741. [PubMed: 8887045]
18. Takikawa H, Manabe T. Primary sclerosing cholangitis in japan--analysis of 192 cases. *J Gastroenterol.* 1997; 32:134–137. [PubMed: 9058310]
19. Prasad GA, Talley NJ. Eosinophilic esophagitis in adults. *Gastroenterol Clin North Am.* 2008; 37:349–368. v–vi. [PubMed: 18499024]
20. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: A population-based study. *Gastroenterology.* 2005; 129:827–836. [PubMed: 16143122]
21. Troncone R, Merrett TG, Ferguson A. Prevalence of atopy is unrelated to presence of inflammatory bowel disease. *Clin Allergy.* 1988; 18:111–117. [PubMed: 3365856]
22. Delgado S, Lacy AM, Filella X, Castells A, Garcia-Valdecasas JC, Pique JM, Momban D, Visa J. Acute phase response in laparoscopic and open colectomy in colon cancer: Randomized study. *Dis Colon Rectum.* 2001; 44:638–646. [PubMed: 11357021]
23. Romero R, Abramowsky CR, Pillen T, Smallwood GA, Heffron TG. Peripheral eosinophilia and eosinophilic gastroenteritis after pediatric liver transplantation. *Pediatr Transplant.* 2003; 7:484–488. [PubMed: 14870899]
24. Foster PF, Sankary HN, Hart M, Ashmann M, Williams JW. Blood and graft eosinophilia as predictors of rejection in human liver transplantation. *Transplantation.* 1989; 47:72–74. [PubMed: 2643234]
25. Kishi Y, Sugawara Y, Kaneko J, Tamura S, Matsui Y, Makuuchi M. Blood eosinophilia after living donor liver transplantation for hepatitis c virus-related cirrhosis. *Transplant Proc.* 2007; 39:1540–1543. [PubMed: 17580184]
26. Polydorides AD, Banner BF, Hannaway PJ, Yantiss RK. Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils. *Hum Pathol.* 2008; 39:832–836. [PubMed: 18430454]

Table 1

Demographic characteristics of eosinophilia-associated UC (EoUC) and control UC patients

Characteristic	EoUC n=16	Control UC n=32	p-value
Age, years, median (IQR)	46.0 (30)	45.5 (27)	0.84
Age group, n (%)			0.92
18 to 29	3 (18.8)	4 (12.5)	
30 to 39	4 (25)	9 (28.1)	
40 to 49	3 (18.8)	6 (18.8)	
50 to 59	1 (6.3)	5 (15.6)	
60 and older	5 (31.3)	8 (25)	
Age at diagnosis, years, median (IQR)	32.0 (22)	30.0 (27)	1.00
Male, n (%)	13 (81.3)	15 (46.9)	0.03
Caucasian, n (%)	15 (93.8)	31 (96.9)	1.00
Cigarette smoking history, n (%)			0.55
Never	10 (62.5)	22 (68.8)	
Former	5 (31.3)	10 (31.3)	
Active	1 (6.3)	0 (0)	

IQR, interquartile range

Dichotomous data are expressed as total number and percentages and were compared using the Fisher's exact test. Continuous data are expressed as medians (interquartile range) and were compared using the Mann-Whitney test. All tests were 2 sided, and *P* values less than 0.05 were considered statistically significant.

Table 2

Clinical characteristics of eosinophilia-associated UC (EoUC) and control UC patients

Characteristic	EoUC n=16	Control UC n=32	p-value
Disease duration, years, median (IQR)	12.5 (5.5)	10 (8)	0.16
10 years or less, n (%)	5 (31.3)	19 (59.4)	0.12
More than 10 years, n (%)	11 (68.8)	13 (40.6)	
Extent of disease			0.015
Pancolitis, n (%)	14 (87.5)	16 (50)	
Left-sided colitis, n (%)	1 (6.3)	14 (50)	
Proctitis or proctosigmoiditis, n (%)	1 (6.3)	2 (6.3)	
Follow-up duration, years, median (IQR)	5.2 (5.3)	4.2 (2.5)	0.042
History of			
IBD hospitalization, n (%)	12 (75)	10 (31.3)	0.006
Colectomy, n (%)	9 (56.3)	5 (15.6)	0.006
Steroid therapy, n (%)	16 (100)	21 (65.6)	0.009
Immunomodulator therapy, n (%)	10 (64.7)	14 (43.8)	0.36
Infliximab therapy, n (%)	6 (37.5)	11 (34.8)	1.00
History of			
Primary sclerosing cholangitis, n (%) or autoimmune hepatitis	7 (43.8)	1 (3.1)	0.001
Colon dysplasia or cancer	2 (12.5)	2 (6.3)	0.59
Drug allergies	8 (50)	16 (50)	1.00
Infections	6 (37.5)	5 (15.6)	0.14

IQR, interquartile range

Dichotomous data are expressed as total number and percentages and were compared using the Fisher's exact test. Continuous data are expressed as medians (interquartile range) and were compared using the Mann-Whitney test. All tests were 2 sided, and *P* values less than 0.05 were considered statistically significant.

Table 3
Frequency and type of clinical scenarios associated with eosinophilia episodes in EoUC patients

		Clinical scenarios					
	Total number of episodes	UC flare	Drug related	Post-operative	Infection	Other	Unknown
Patient							
1	3			1, colectomy	1, abdominal abscess		1
2	2			1, ileostomy takedown	1, abdominal abscess		
3	2					1, esophageal rupture	1
4	11	4			1, osteomyelitis		6
5	4			1, colectomy		1, pneumonia	2
6	3	1		2, liver transplant for PSC			
7	3		1	1, liver transplant for AIH		1, ascites	
8	2			1, liver transplant for PSC	1, <i>C. difficile</i>		
9	10	2				5, PSC	3
10	3			1, liver transplant for PSC		1, liver rejection	1
11	6					6, PSC	
12	3			2, colectomy, Ileostomy takedown		1, PSC	
13	3			2, colectomy, Ileostomy takedown		1, pouchitis	
14	7	1				2, migraines	4
15	5	1		1, colectomy			3
16	2			2, colectomy abdominal hernia repair			