Eosinophilic-Crohn overlap colitis and review of the literature

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Abstract

Eosinophilic colitis is an idiopathic inflammation of the alimentary canal and is characterized by infiltration of the intestinal wall by eosinophils, massive submucosal edema, and peripheral eosinophilia. However, the presence of eosinophils in a colon biopsy requires thorough searching for secondary causes and eosinophilic colitis remains a diagnosis of exclusion.

A 67-year-old male patient underwent a diagnostic ileocolonoscopy because of recurrent episodes of diarrhea for the last six months. Colonoscopy revealed a normal terminal ileum while in the entire colon an erythematous mucosa with very slight edema on a continuous pattern that was more pronounced in the left colon. The laboratory workup demonstrated eosinophils slightly elevated, biochemical tests were unremarkable and further clinical and laboratory workup was unremarkable. Histology showed overlapping findings of eosinophilic colitis and Crohn’s colitis.

Patient started on mesalazine 2.4 with very good results.

A review of the literature shows that the spectrum of eosinophil involvement in inflammatory bowel disease as well as in eosinophilic colitis is largely varying, including also some exceptional cases that parallel the case described herein.

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1. Introduction

The presence of activated tissue and peripheral blood eosinophils in chronic inflammatory bowel disease (IBD) has been reported since many years. Moreover, different regulations of eosinophil activity in Crohn’s disease (CD) compared with ulcerative colitis (UC) have been demonstrated. In addition, eosinophil granulocytes in the rectal mucus and increased fecal or gut lavage fluid eosinophil cationic protein have been shown to be present in patients with IBD.
Of interest, allergic symptoms and respiratory symptoms including cases with eosinophilic pneumonia, bronchial hyperreactivity, abnormal lung function tests and skin prick test positivity were found to be more common among the IBD patients in comparison with the controls. Of interest, CD patients without any clinical respiratory involvement have airway eosinophilia while the percentage of sputum eosinophils is significantly different between UC patients with proctitis and pancolitis.

Eosinophilic gastroenteritis, an idiopathic inflammation of the alimentary canal, is characterized by infiltration of the intestinal wall by eosinophils, massive submucosal edema, and peripheral eosinophilia. It is generally confined to the gastric antrum and proximal small intestine. The colon is rarely cited as a site for the condition while eosinophilic ileocolitis is extremely rare. Eosinophilic ileitis must be always differentiated from Crohn's disease, infectious diseases, spondyloarthopathies, vasculitides, ischemia, neoplasms, food induced allergy and medication-induced lesions.

Eosinophilic colitis has a broad differential diagnosis because colon tissue eosinophilia often occurs in many other conditions, such as inflammatory bowel disease, neoplasms, parasitic infection (pinworms, roundworms, or whipworms), allergic colitis, drug-induced reactions (clozapine, carbamazepine, rifampicin, non-steroidal anti-inflammatory agents, tacrolimus, and gold), inflammatory bowel disease, and various autoimmune connective tissue diseases (including scleroderma, dermatomyositis and polymyositis), as well as with allogeneic bone marrow transplantation and the rare Tolosa-Hunt syndrome that features inflammatory ophthalmoparesis. Therefore, the presence of eosinophils in a colon biopsy requires thorough searching for secondary causes that may be specifically treated with antibiotics or dietary and drug elimination and EC remains a diagnosis of exclusion.

Herein is described a case of a patient with chronic diarrhea who was diagnosed with overlap eosinophilic and Crohn's colitis.

### 2. Case report

A 67-year-old male patient underwent a diagnostic ileocolonoscopy in our department because of recurrent episodes of diarrhea for the last six months. Colonoscopy revealed a normal terminal ileum while in the entire colon an erythematous mucosa with very slight edema on a continuous pattern that was more pronounced in the left colon; at very careful bowel inspection there were no ulcers, diverticula, focal inflammatory lesions or adenomas. Multiple biopsies were taken and the patient empirically started 2.4 gr of mesalazine.

The otherwise not smoker healthy patient denied any history of abdominal pain, bloody stool, and a family history of inflammatory bowel disease, pulmonary and allergic symptoms.

The patient did not take any medication on a long-term basis prior to colonoscopy including heavy metals and NSAIDs. There was no history of recent radiation therapy for a contiguous cancer. The patient originated from our area and he did not make any trip abroad or change his food habits recently. No other patients presented with similar complaints so far.

The laboratory workup demonstrated eosinophils slightly elevated (6400 cells per mm³, 6.4%), erythrocyte sedimentation rate at 22 mm/h and negative C-reactive protein. Biochemical tests were unremarkable and chest and abdominal computed tomography did not reveal any other metastatic lesions. There was no evidence for collagen vascular diseases.

Histology showed overlapping findings of eosinophilic colitis and Crohn's colitis (Figs. 1–4). There were no other features of chronicity such as Paneth cell metaplasia and basal plasmacytosis present in the colonic biopsies. The distribution of the histological abnormalities was rather symmetrical over the colon. Biopsies from the terminal ileum did not reveal something remarkable.

Subsequent full work up for allergy of any type or parasites proved negative and the patient was given the diagnosis of colitis with overlapping characteristics of that of eosinophilic and of Crohn's colitis.

Patient was advised to continue mesalazine and was advised to undergo a follow up endoscopy after six months in the hope that in that time we will be able to provide a conclusive diagnosis.

### 3. Discussion

A review of the literature shows that the spectrum of eosinophil involvement in IBD and eosinophilic gastroenteritis is largely varying, including also some exceptional cases that parallel the case described herein.

In the upper gastrointestinal tract an interesting case of a patient who presented with multiple small submucosal nodules with granulomatous inflammation in the minor salivary glands of the oral cavity is described. Sarcoïdosis, Crohn's disease, tuberculosis and atypical mycobacterial infection were not identified by medical examination and authors suggested the term 'allergic granulomatous sialadenitis'.

Another interesting case of eosinophilic esophagitis with Crohn's disease has been described as a new association or an overlapping immune-mediated enteropathy.

In the lower gastrointestinal tract a case of an inflammatory fibroid polyp characterized as eosinophilic granuloma and Crohn's disease located in the ileum has been reported. Another case of a child with Crohn's disease who developed a eosinophilic gastroenteritis has been reported. Although symptoms of eosinophilic gastroenteritis at this child could mimic those of Crohn's disease, laboratory, radiographic and histologically studies were clearly different with peripheral blood eosinophilia, high serum IgE level and normal C-reactive protein and erythrocyte sedimentation rate. Eosinophilic gastroenteritis was due to bovine serum albumin (BSA) hypersensitivity, confirmed with skin tests, serum levels to specific IgE and IgE-immunoblotting and a strict meat-free diet was started, with progressive relief of symptoms and decrease of eosinophil count twelve months later.

![Figure 1](Image) Eosinophilic infiltration of lamina suggesting eosinophilic colitis.
A case of a patient undergoing hemicolectomy due to eosinophilic gastroenteritis involving the ileocecal area and who on follow up had not shown evidence of recurrence or extension of the disease to the stomach or proximal small intestine clearly implies a parallelism to that of Crohn’s disease potential for post-surgery recurrence.

Atypical syndromes implicating similar phenotypes or overlap of Crohn’s disease and eosinophilic gastroenteritis are cases of primary sclerosing cholangitis associated with eosinophilic colitis or colonic Crohn’s disease and marked eosinophilia or of diffuse eosinophilic fasciitis, atypical rash, and chronic inflammatory disease of the colon or of eosinophilic colitis with perianal disease. Finally an interesting couple case of eosinophilic enteritis in the husband and Crohn’s disease in the wife has been reported.

In this case there are several histological characteristics favoring either the eosinophilic or the Crohn’s disease diagnosis and supporting this overlap. However, studies on the frequency and role of intestinal eosinophils in patients with inflammatory bowel disease have yielded conflicting results. Histopathology studies have contributed to a better understanding on the role of eosinophils and activated eosinophils in IBD.

Eosinophils are normal constituents of the mucosa of the gastrointestinal tract and there has been no definitive determination of the number of eosinophils that can be defined as normal. They are not distributed uniformly along the length of the bowel, and in the large intestine, it is well recognized that they are usually more numerous in the cecum and ascending colon than elsewhere. Normal values for tissue eosinophils vary widely between different segments of the colon, ranging from less than 10 eosinophils per high-power field in the rectum to more than 30 in the cecum, thus location of the biopsy is critically important for interpretation of findings.

A diagnosis of EC is made if the eosinophils infiltrate the crypts or there are focal collections of 10 or more eosinophils per high power field, in the absence of other identifiable abnormalities. EC is characterized by a florid tissue and peripheral blood eosinophilia with some histopathological similarities to chronic inflammatory bowel disease. Unlike CD, granulomas, pseudopyloric metaplasia, architectural distortion, and fibrosis are usually not features of EC. Furthermore, inflammatory infiltrate of CD is usually mixed and not exclusively eosinophils. The crypt architectural distortion of ulcerative colitis is not also present in EC. In some cases, the patients will eventually be diagnosed with CD. However, in other patients the cause of changes is never determined.

In our case, histopathological examination showed focal distortion of the architecture without mucin depleted or even reduced. On the lamina

![Figure 2](image1.png)  The inflammatory infiltrate crosses the muscularis mucosae, suggesting Crohn’s disease.

![Figure 3](image2.png)  The arrows in the panel show crypt abscesses that consists almost entirely of eosinophils. There is also an increased number of eosinophils in the lamina propria.
Figure 4  Mucosal biopsy with mild glandular irregularity. There is an intense inflammatory infiltrate in the submucosa, which crosses the muscularis mucosae, suggesting Crohn's disease.


In this patient food-induced allergy cannot definitely be excluded although no positive history or allergy test was supportive of this probability. The most typical presentation of eosinophilic colitis is allergic eosinophilic proctocolitis, which affect babies under 3 months and responds to an immune reaction triggered by the intake of foreign proteins, especially cows' milk proteins, even if they are consumed by the mother and excreted with breast milk. Analytical alterations are not usually found and allergic skin tests and specific IgE are negative reinforcing the idea that food allergy is not usually mediated by type-1 immune reactions.40–42

Furthermore the answer to the enigma whether Crohn's disease is a food-induced disease still cannot be answered. In fact, food-induced immune responses cause or influence a number of intestinal diseases. There are diseases where food is the primary factor in the pathogenesis, such as food allergy and gluten-sensitive enteropathy. Furthermore, allergic reactions may play a role in eosinophilic esophagitis and eosinophilic gastroenteritis. In IBD food influences the disease by the modulation of various factors such as intestinal bacterial flora or the inflammatory cascade and this may have some significance in the perpetuation of intestinal inflammatory processes in patients with Crohn's disease.43

Eosinophil accumulation and activation44 are also characteristic features of inflammation in host defense against parasites such as ascariasis where an IgE-mediated response is characterized by a dramatic increase in mucosal-type cells and eosinophils in both the mucosa and the deeper layers of the intestinal wall.45 By contrast, in a study with immunohistological assessment of intestinal eosinophil activation in patients with eosinophilic gastroenteritis and IBD it has shown that in IBD patients eosinophils seem to be activated but their number is not or only slightly elevated compared to controls.46

Interesting data has been also accumulated supporting that eosinophils are functionally involved in the pathophysiology of IBD. Eotaxin is a chemokine with potent and selective chemotactic activity for eosinophils and two serum studies47,48 and one in full thickness bowel wall specimens49 showed elevated serum eotaxin levels in IBD patients. Another two studies have suggested an important role for eosinophil protein X50 in feces and for tissue content51 of eosinophil cationic protein in IBD. In fact, mucosal infiltration by eosinophils may represent a pivotal phenomenon in early IBD or in acute forms of the disease the so-called "acute self-limited colitis".52

A study to in patients presenting with symptoms of inflammatory bowel disease showed that eosinophils together with granulomas, solitary giant cells, pseudopyloric gland metaplasia, and a disturbed villous architecture were the most important lesions observed in early Crohn's disease and were contributive for this diagnosis.53 In two other cases dense eosinophilic infiltration mimicking eosinophilic colitis preceded ulcerative colitis.54

Finally there is a potential role for eosinophils in CD recurrence. In fact, it has been demonstrated that there is an increased response of blood eosinophils to various chemotactic agents, including eotaxin, in clinically quiescent Crohn disease55 and activated eosinophil and interleukin 5 expression has been demonstrated in early recurrence of CD.56

The overlapping of those idiopathic diseases of the colon that was described herein may reflect their overlapping etiology. In fact, the gastrointestinal tract is continuously in contact with a multitude of antigens and therefore contains a well-developed defense mechanism.57 From initial inflammatory reaction until disease manifestation a large individuality seems to be present regarding the perpetuation as well as the end-point of inflammation.

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