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Review Article

Eosinophilic colitis: A clinical review

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ABSTRACT

Eosinophilic colitis is a rare entity characterized by the presence of a high eosinophilic infiltrate into the colonic wall in symptomatic patients, more often presenting with abdominal pain or diarrhea. These characteristics distinguish eosinophilic colitis from primary colonic eosinophilia, in which patients are asymptomatic. Primary colonic eosinophilia does not need any therapy, while eosinophilic colitis requires a strict treatment, similar to that of the more codified chronic intestinal inflammatory diseases. To date the lack of codified guidelines regarding the diagnostic criteria and the eosinophil threshold values for each colonic segment are the main diagnostic challenge for eosinophilic colitis. In addition, eosinophilic colitis is a diagnosis of exclusion, once all other causes of colonic eosinophilia (food allergens, infections, drugs, etc.) have been excluded. Several treatment options are available for eosinophilic colitis, although the evidence for most of them is limited to case reports and small case series.

We examine the epidemiology, etiology, pathophysiology, diagnostic criteria and therapeutic options of eosinophilic colitis reporting recent evidence from the current literature.

1. Background

Eosinophilic colitis (EC) is a rare condition included in the group of eosinophilic gastrointestinal disorders (EGIDs), that are characterized by a high eosinophilic infiltrate in the gut wall, without evidence of other causes [1,2]. In the EC there is a segmental or diffuse intense eosinophilic infiltration in the colon [3,4].

The definition of EC is still object of debate. For most authors the term "eosinophilic colitis" should be reserved to symptomatic patients, while in the case of asymptomatic patients with a significant increase in colonic eosinophils, it is preferred to talk about primary colonic eosinophilia (PCE) [5]. However, PCE remains a poorly characterized condition that pathologists may consider when "greater than normal" numbers of eosinophils are found in the colonic mucosa [2,6]. In addition, there are no guidelines to define an excessive number of eosinophils in the colonic biopsies, because there are not specific limits for normality [5]. To date, EC is still an obscure entity and there is no clear understanding of its real clinical impact or natural history [2]. This review examines etiology, pathophysiology, diagnostic criteria and therapeutic strategies of EC. We report recent evidence from the current literature.

2. Epidemiology

The epidemiology of EC is difficult to study, partly due to the lack of well-defined diagnostic criteria [7]. Eosinophilic colitis seems to have a bimodal age distribution, with a first peak in neonates and a second peak in young adulthood [8,9]. A recent review of a population-based database in the USA, including more than 35 million of children and adults, reported an overall prevalence of EC of 2.1 per 100,000 subjects, with a prevalence of 2.3 per 100,000 in adults and 1.6 per 100,000 in children [10]. The prevalence of eosinophilic gastrointestinal disorders seems to be higher in urban and suburban than in rural areas [11], in women and in white individuals [8,10].

3. Etiology

The specific etiology of primary EC is unclear. There is undoubtedly an interaction between genetic and environmental factors considering that 16% of patients with EGIDs have a family member with a similar disorder. Several authors associated EC with allergic diseases [8] such as rhinitis, asthma, sinusitis, dermatitis, food allergies, eczema, or urticarial [10] or atopic conditions [12,13]. An

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allergic component is likely to be present in all EGIDs considering that 80% of patients have a coexistent atopic disease, while 62% experience specific food sensitivities [14,15].

Primary EC is a diagnosis of exclusion [1], since colonic eosinophilic infiltrate can also occur secondarily to several conditions such as parasitic and helminthic infections (i.e. Strongyloides stercoralis, Enterobius vermicularis, and Trichuris trichiura) [16–19] and use of drugs such as clozapine [4], carbamazepine [20], rifampicin, gold [21], and naproxen [22]. Liver transplant recipients treated with tacrolimus as an immunosuppressive agent are also at risk of developing colonic eosinophilia, and an improvement of symptoms occurs when the immunosuppression is reduced [23]. Eosinophilic colitis also can occur secondarily in association with inflammatory bowel diseases (IBD) [24], coeliac disease and autoimmune diseases (lupus erythematosus, scleroderma and Churg-Strauss syndrome) [25] and with the hyper-eosinophilic syndrome [26].

4. Pathophysiology

Although the physiologic functions of eosinophils remain largely unknown, they are known to be involved in host immune response to infections, tissue remodeling, tumor surveillance, and maintenance of other immune cells [27].

Eosinophils are primarily tissues-swelling cells and they are several hundred-fold more abundant in tissues than in the blood [28]. In healthy individuals, eosinophils can be found in the spleen, lymph nodes, thymus, and are normally found in the mucosa of all the gastrointestinal (GI) tract except for the esophagus [27].

Homeostatic eosinophils mainly reside in the lamina propria of the small intestine [29] protecting against pathogenic parasites and bacteria. These cells are selective in their response to pathogens, allowing some to reside in the mucosa and thereby regulating the intestinal microbiome and contributing to tissue homeostasis [30].

Eosinophils respond to several stimuli including non-specific tissue injury, allergens and infections. Recruitment and activation of eosinophils to sites of inflammation is regulated by cytokines, including IL5, IL13, IL4 and tumor necrosis factor (TNF) produced by activated Th2 and mast cells [31,32]. Activation results in degranulation, upregulated cytokine production, and IgE production. Pre-formed granules contain four major cationic proteins, all of which are cytotoxic: eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin and major basic protein. Eosinophils produce leukotriene C4, which is then metabolized to LTD4 and LTE4, potent smooth muscle constrictors, and a wide range of cytokines that potentiate the inflammatory response. Eosinophilic colitis in infants seems to be an IgE-associated disorder with mast cell accumulation and degranulation in the colonic tissue; this condition could be associated with breast-feeding or protein hydrolysate formula-feeding [1]. On the other hand, in adults EC is more likely a non IgE-associated disorder, acting through a CD4 (+) Th2 lymphocyte-mediated mechanism [1].

Thus, the increased eosinophilia in EC appears to be triggered by the combination of a genetic predisposition, dysbiosis, and environmental factors (i.e, ingested or inhaled allergens) [33], but further research is needed to define the underlying pathogenesis of these complex disorders [34].

5. Clinical presentation

Eosinophilic colitis is a heterogeneous entity, ranging from an acute self-limited bloody diarrhea in otherwise healthy infants to a chronic colitis with abdominal pain and/or chronic diarrhea in young adults [1]. Other symptoms include nausea, vomiting, GI bleeding, bowel obstruction, malabsorption, weight loss or ascites [17]. Clinical features are related to the layers of bowel with eosinophilic infiltration [35]. Mucosa predominant EC, which is the most common form, is associated with mucosal injury and presents with malabsorption, diarrhea and protein losing enteropathy. The less frequent transmural disease presents more dramatically with colonic wall thickening and features of acute intestinal obstruction (intussusception or cecal volvulus) or even perforation [20]. Serosal disease, a very rare form, presents with ascites, in which eosinophils are the predominant cell type in up to 95% of cases, and is associated with good prognosis [3,4,36]. However, distinguishing between various forms can occasionally be challenging as endoscopic biopsies do not include submucosa, muscularis propria or serosa not allowing a complete assessment of the extent of the eosinophilic infiltration [9].

The progression of disease in EC is variable: a considerable number of patients have just one episode without relapse, whereas others are affected by a relapsing-remitting or chronic disease [34]. In particular, the mucosal type appears to be associated with chronic persistent symptoms without remission, the muscular type is associated with recurrence and relapses of symptoms, while the serosal type has the best prognosis with a single flare and usually no relapses [36]. Eosinophilic colitis in infants is a relatively benign, it is frequently a food-related entity and dietary elimination of the aggressor often resolves the disorder within days, whereas adolescent or older patients require more aggressive medical management [1].

6. Diagnosis

The diagnosis of EC is challenging [1]. A reasonable approach should require both a clinical and histological diagnosis of EC, associating symptoms referable to colonic dysfunction with colon biopsies showing excess eosinophils [5], in patients without other causes of colonic eosinophilia, such as infectious colitis or IBD [37].

Allergic skin testing (AST) and radioallergosorbent tests (RASTs) are useful in detecting IgE-mediated responses to inhaled or ingested allergens, although ASTs lack sensitivity and specificity and show a high false-positive rate [1]. Peripheral eosinophilia (an absolute eosinophil count >500 cells/microL) may be absent in 20% of patients. A stool sample should be analyzed to exclude parasitic infections [38].

Radiological findings in children with EC are scars; Brandon et al. [37] examined CT colonic and extracolonic findings in seven children with EC, observing in five of them that the cecum or ascending colon were the predominant segments involved with less severe or no involvement of the distal colon. In addition, the small bowel was either normal or involved to a lesser degree than the colon in all of these children [37]. Abnormal CT findings are often nonspecific and present in 60-70% of cases in adults. Imaging may show nodularity of the bowel wall, circumferential colonic wall thickening, long-segment thickening from the ascending to the descending colon, and mucosal fold thickening and the “araneid-limb-like” sign in the ascending and transverse colon. This latter sign is due to diffuse mucosal thickening and it occurs when contrast within the mucosal sinuses in the longitudinal section of the bowel on CT are prominent. Ascites may also be seen in some cases [39,40].

These radiological aspects should be considered in the differential diagnosis with inflammatory and infectious colitis.

Endoscopy in most cases shows generally normal mucosa, helping to distinguish EC from other forms of colitis [41]. Non-specific endoscopic findings, such as patchy areas of mucosal edema, punctate erythema [6], elevated lesions, pale granular mucosa and aphthous ulceration, may be seen, although these findings are uncommon and should not be relied on [5].

From an histological point of view, the presence of edema, eosinophil degranulation, involvement of submucosa and muscu-

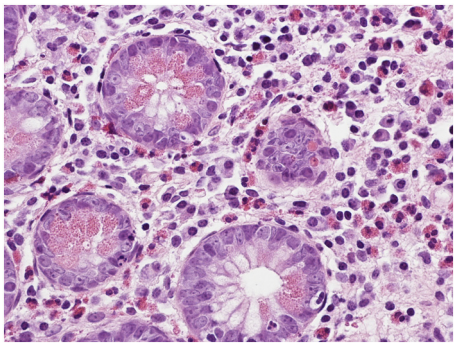

Fig. 1. Eosinophilic colitis histological section. Photography with objective at 40×. Biopsy was fixed in formalin, embedded in paraffin and stained with hematoxylin-eosin.

laris mucosae and abnormal distribution of eosinophils have been found to be useful features for diagnosing EC (Fig. 1) [42]. Crypt abscesses and lymphonodular hyperplasia may also be evident [15,43–45]. Eosinophils are normally present in colon mucosa and are most abundant in the right colon of both children [46–48] and adults [5]. Therefore, using a single threshold value to identify increased eosinophil density is less accurate and potentially misleading, compared to applying threshold values appropriate for each colon site (right, transverse, left, rectosigmoid).

A reference value to establish an excess of eosinophils is a number > 50/HPF in the right colon, >35/HPF in the transverse colon and > 25 per HPF in the left colon [49]. Other threshold values proposed is a count of eosinophils > 65/HPF in the right and left colon [50].

These eosinophils numbers are, however, only suggestions derived from case series and have not been validated in different populations yet, as is the case for eosinophilic esophagitis [51], and currently, no formal guidelines exist for mucosal biopsy diagnosis. It must be appreciated that eosinophils are normal constituents of the gut and that numbers might vary widely among individuals; region, climate, age, exposure to food allergens, infectious agents, use of drugs and other autoimmune diseases should all be taken into consideration when assessing biopsy samples [39]. Moreover, a patchy distribution of the disease may be present and the diagnosis can be missed; therefore, more than one complete colonoscopy may be required to obtain random biopsy samples from the terminal ileum and each segment of the colon [52–54].

7. Treatment

Eosinophilic colitis in infants is a rather benign entity and is food-associated; therefore, dietary elimination of the triggering allergen often resolves the disorder within days. Adolescents and older patients require more aggressive medical management [1]. If no secondary cause of eosinophilia is found, and a diagnosis of primary EC is made, several treatment options are available, although the evidence for most of them are limited to case reports and small uncontrolled case series [34].

7.1. Role of diet

Diet therapy is the first therapeutic approach for GI diseases caused by eosinophils [39]. The treatment of EC applying a rigorous elemental diet has shown to be effective in 75% of infants [55], but its use is limited especially by the scarce compliance of children and adults [34]. However, there is still no clear evidence that the elimination of the main food antigens could be effective in adults with EC [6].

7.2. Corticosteroids

Corticosteroids are used as first-line drug therapy in EC if dietary therapy fails to achieve an adequate clinical response or is impractical [39]. The beneficial effects of corticosteroids in eosinophilic disorders are largely mediated by the inhibition of eosinophil growth factors, such as IL-3, IL-5 and GM-CSF.

Oral prednisone at doses of 20–40 mg per day for 2 weeks has been shown to induce clinical remission in most patients [52], although higher doses (0·5–1 mg/kg) are suggested in some reports [39]. However, there are no randomized controlled trials to date on the efficacy of steroids in EGIDs or specifically in EC. Patients in whom symptoms relapse during or after drug tapering might require ongoing maintenance treatment with low-dose prednisone (5–10 mg per day, or the minimum required dose to maintain response) [39,56] or budesonide (3–9 mg per day) [57].

7.3. Steroid-sparing agents

Mesalazine has been reported to be effective in some cases of EC [2]. Immunomodulatory agents, such as azathioprine [58] and anti-TNF agents (infliximab and adalimumab) [59], have been tried in severe, steroid-refractory or steroid-dependent EC with encouraging results.

Chemokines such as eotaxin may be involved in eosinophil recruitment. This provides the rationale for using immunomodulatory agents such as azathioprine or 6-mercaptopurine to down regulate or inhibit these mediators, resulting in less eosinophilic infiltration and symptomatic improvement [13].

The role of Montelukast, a leukotriene receptor antagonist, has yet to be evaluated in EC, particularly in terms of steroid-sparing benefit [1]. Other options include mast-cell stabilizers, such as sodium cromoglycate and ketotifen [60]. Sodium cromoglycate, alone or in combination with ketotifen, shows potential as induction and maintenance therapy for patients with EGIDs, with no report so far about its effectiveness in treating EC patients [61,62].

A novel antibody directed against CCR3, an eotaxin receptor expressed by eosinophils that facilitates their recruitment to the sites of inflammation, has been shown to decrease eosinophilic inflammation and diarrhea in a mouse model [34,63].

7.4. Faecal microbiota transplantation

Faecal microbiota transplantation has been successfully used in one patient with eosinophilic enterocolitis affecting the ileum and colon, whose disease was refractory to enteral nutrition, azathioprine, steroids, and surgical resection [64]. However, it remains unclear whether faecal microbiota transplantation could cure EC and maintain long term clinical remission if corticosteroids were not given.

7.5. Surgery

Surgery should be limited for the treatment of severe EC complications, such as bowel obstruction, volvulus, intussusception and perforation [65]. Segmental colonic resection is recommended with no clear consensus or evidence to support primary anastomosis or diversion [65].

8. Conclusion

Eosinophilic colitis remains a rare entity, whose natural history and pathophysiology is still unclear, currently lacking codified guidelines for the diagnosis and treatment. In particular, there is

still a lack of well-defined threshold values for the diagnosis of EC. Therefore, future studies including a large sample of patients should aim to define and validate specific diagnostic criteria and establish the most appropriate treatment for the disease.

Conflict of interest

None declared.

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