

Eosinophilic Enteritis

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Key Words

Eosinophils · Gastroenteritis · Intestinal mucosa · Corticosteroids · Natural history

Abstract

Background: Eosinophilic enteritis, also known as eosinophilic gastroenteritis, is a rare primary eosinophilic gastrointestinal disorder (EGID) of unknown etiology characterized by the presence of an intense eosinophilic infiltrate on histopathology of the intestinal mucosa. **Key Messages:** The etiology of eosinophilic enteritis remains obscure. There is growing evidence to support the role of aeroallergens and food allergens in the pathogenesis of this disorder as children and adults with EGIDs often have positive skin testing for food allergens and a familial history of allergic diseases. Moreover, significant progress has been made in elucidating that EGIDs involve mechanisms that fall between pure IgE-mediated and delayed Th2 type responses. Preclinical studies have identified a contributory role for the cytokine IL-5 and eotaxin chemokines, providing a rationale for specific disease therapy. Eosinophilic enteritis causes a wide array of gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, bloating or ascites, and its diagnosis requires a high degree of clinical likelihood given the non-specific presentation and physical examination findings. The Klein classification arbitrarily divided patients with eosino-

philic enteritis into those with predominantly mucosal, muscle layer or subserosal disease relying on the concept that clinical presentation is dependent on the predominant involved layer of the gastrointestinal tract. Main therapeutic options are represented by oral corticosteroids for a short period with good efficacy. Antihistaminic drugs and sodium cromoglycate have also been used to treat patients with eosinophilic enteritis. **Conclusion:** Eosinophilic enteritis is generally considered as a benign disease with no relapse, but half of the patients may present a more complex natural history characterized by unpredictable relapses and a chronic course.

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Introduction

Eosinophilic enteritis, also known as eosinophilic gastroenteritis, is a rare gastrointestinal disorder of unknown etiology characterized by an intense infiltration of the intestinal wall by eosinophils [1, 2]. It is part of the primary eosinophil-associated gastrointestinal disorders (EGIDs) which also include eosinophilic esophagitis and allergic eosinophilic colitis (table 1). Described for the first time by Kaijser in 1937 [3], eosinophilic enteritis is defined by the presence of gastrointestinal symptoms associated with an eosinophil-rich infiltration of the intestinal mu-

Table 1. Primary EGIDs

Forms	Definition	Main clinical characteristics
<i>Eosinophilic esophagitis</i>		
Atopic	Eosinophilic infiltration of the esophagus mucosa without other intestinal segments involved	Dysphagia
Nonatopic		Vomiting
Familial		Food impaction
<i>Eosinophilic gastroenteritis</i>		
Mucosal	Gastrointestinal symptoms Eosinophilic infiltration of one or more intestinal segments	Abdominal pain
Muscular		Diarrhea
Suberosal		Obstruction Ascites
<i>Eosinophilic colitis</i>		
Atopic	Children	Diarrhea
Nonatopic	Eosinophilic infiltration of the colon Atopy or cow milk protein allergy	Rectal bleeding

cosa without causes of secondary intestinal eosinophilia [4]. Eosinophilic enteritis may affect the entire digestive tract from the esophagus to the rectum, and eosinophils can invade the intestinal wall from the epithelium to the serosa with a variable depth. According to the Klein classification [1] and the predominant intestinal layer involved, eosinophilic enteritis is divided into three distinct anatomical forms including predominant mucosal disease, predominant disease of the muscle layer and serosal disease. Recently, some progress has been made in the understanding of the pathogenesis of eosinophilic enteritis involving allergy and delayed Th2 response in the development of the disease [5]. Also, recent studies investigating recruitment and activation of eosinophils have allowed the development of new therapeutic strategies in EGIDs such as monoclonal antibodies directed against IL-5 (mepolizumab) [6]. Mepolizumab is currently used for the treatment of hypereosinophilic syndrome, asthma and eosinophilic esophagitis [7–9]. Eosinophilic enteritis is still away from this new treatment because of its rarity and its benign course with good response to corticosteroids in most cases. Herein, we will review the recent findings regarding eosinophilic enteritis pathogenesis, epidemiology, clinical characteristics and treatment.

Pathogenesis of Eosinophilic Enteritis

The eosinophilic granulocyte is characterized by a lobed nucleus and the presence of specific intracytoplasmic granules having a high affinity for acid dyes such as eosin. Eosinophil granules contain acidophilic cationic

proteins that are responsible for the specific eosin staining including major basic protein, eosinophil cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin [10]. These cationic proteins are able to disrupt membranes and are toxic to helminths and bacteria. They also have an RNase activity that could neutralize viruses. Moreover, cationic proteins are toxic to different cell types from numerous organs, including bronchial epithelium, keratinocytes, pneumocytes, gut epithelium and could activate numerous cells such as eosinophils themselves, basophils, neutrophils and mast cells. Under activation, the eosinophils are able to secrete these granules and act as a major inflammatory cell involved in allergic diseases and parasitic infections [11].

Eosinophils are produced in the bone marrow, where they undergo a period of maturation before reaching the bloodstream. Differentiation, proliferation and presence of eosinophils in the peripheral blood are dependent on GM-CSF, IL-3 and IL-5 signaling pathways [12]. From there, eosinophils migrate to different organs where they are normal resident, including thymus, uterus, mammary glands and gastrointestinal tract. This physiological homing of eosinophils is under the control of eotaxin-1, a major eosinophilopoietin [12]. In the gastrointestinal tract, eosinophils are located in the lamina propria of every segment of the gut except the esophagus. At baseline, eosinophils do not cause any inflammation or tissue damage and allow for effective surveillance and protection against parasitic infections [2].

Eosinophils are activated by nonspecific tissue damage, allergens or infections and are responsible for gastrointestinal lesions and symptoms observed in eosinophilic

enteritis [13, 14]. Activation of eosinophils will trigger degranulation leading to the direct cytotoxicity of cationic proteins and secretion of IgE [2]. Activated eosinophils will also release numerous proinflammatory cytokines such as IL-4, IL-5, IL-13 and RANTES, amplifying the local inflammatory response and recruiting immune cells to the site of inflammation [15]. Currently, eosinophil is considered as a multifunctional leukocyte expressing a wide array of surface markers that were previously thought to be exclusively expressed by other cell types including TLRs, gamma delta TCR (innate immune receptors) and MHC class II molecules. Although eosinophils were before defined only as a terminal effector of the innate immune response, their ability to secrete cytokines and chemokines and to interact with lymphocytes clearly shows their role in the activation and action of the adaptive immune response [15].

The initial stimulus leading to eosinophilic enteritis is still unknown, and both direct IgE-mediated response and delayed Th2-adaptive response are suspected to be involved in the development of eosinophilic inflammation of the intestinal mucosa [5].

Epidemiology of Eosinophilic Enteritis

Eosinophilic enteritis is a rare condition. Since its first description by Kaiser in 1937, less than 400 cases have been reported in the literature, either in the form of clinical cases or in single-center retrospective series [1, 4, 16–21]. Its prevalence is estimated to be 1 per 100,000 population [4]. Diagnoses of eosinophilic enteritis have been reported in different countries from North America to South East Asia and Japan. Eosinophilic enteritis is probably misdiagnosed because of nonspecific gastrointestinal symptoms which do not lead systematically to endoscopy with biopsies. Also, the time between first symptoms and diagnosis may be long, with more than 2 years of delay in some case series. Eosinophilic enteritis can affect all age groups, with a peak incidence between the third and fourth decades, and presents a male predominance [4, 20].

The allergic origin of eosinophilic enteritis has long been suspected and is still debated. Patients with eosinophilic enteritis have a personal or family history of atopy and/or allergy in 25–75% of cases [22]. The elevation of IgE levels in the blood also argues in favor of an allergic origin of eosinophilic enteritis. Several patients with eosinophilic enteritis or other EGIDs present positive skin test to food allergens. Moreover, allergy survey based on

dietary questionnaire may identify some products possibly implicated in the development of the eosinophilic disease.

Clinical Characteristics of Patients with Eosinophilic Enteritis

Gastrointestinal symptoms of patients with eosinophilic enteritis are nonspecific. The main inaugural symptoms are abdominal pain, nausea and/or vomiting, diarrhea and ascites [4, 20, 21]. Other gastrointestinal symptoms may be indicative such as dysphagia, rectal bleeding or jaundice. Eosinophilic enteritis may also be revealed by a complication requiring surgery (obstruction, stenosis, peritonitis) [23].

The clinical presentation of eosinophilic enteritis varies with the depth of the eosinophilic infiltration through the bowel wall. In 1970, Klein et al. [1] classified the eosinophilic enteritis into three different forms according to the predominantly involved intestinal layer: the mucosal, muscular and subserosal forms of eosinophilic enteritis. This classification of eosinophilic enteritis was established from the study of a group of patients in whom the depth of the lesion was evaluated on surgical specimens. When the eosinophilic infiltration involves predominantly the mucosa, patients have symptoms related to mucosal inflammation (diarrhea, abdominal pain, gastrointestinal bleeding) as well as signs of malabsorption and protein-losing enteropathy. When the muscular layer is predominantly involved, patients present mostly obstructive signs and symptoms. A predominant subserosal infiltration is characterized by the presence of an ascites which is rich in eosinophils associated with bloating and abdominal pain [1]. In the literature, the predominantly mucosal disease represents about 50% of patients with less muscular and subserosal disease. Talley et al. [4] reported a proportion of mucosal, muscular and subserosal disease of 57.5, 30 and 12.5%, respectively [4]. In our experience, there was a predominance of mucosal forms (44%) with a higher proportion of subserosal forms (49%) and few muscular diseases (12%) [20]. Variation in the proportion of anatomical patterns in eosinophilic enteritis may be due to limitation in the evaluation of the depth of infiltration in patients without surgical resection.

Clinical manifestations of eosinophilic enteritis also depend on the distribution of eosinophilic infiltration along the digestive tract. Esophageal involvement is systematically associated with the infiltration of one or more other intestinal segments, and its frequency is probably

underestimated due to the lack of systematic esophageal biopsies in the different series of eosinophilic enteritis. Infiltration of esophagus mucosa is responsible for esophageal motility disorders leading to dysphagia [13]. The stomach and proximal small intestine are reported to be the most frequently involved intestinal segments, in about 40–80% of cases, and systematic biopsies to look for eosinophilic infiltration of the mucosa in patients with gastrointestinal symptoms are required [4, 20, 24, 25]. Eosinophilic infiltration of the proximal small intestine may be associated with protein-losing enteropathy, malabsorption and iron deficiency anemia. Colonic localization seems more rarely reported [4]. The frequency of this involvement is probably underestimated, and in a case series where colonic exams with biopsies were almost systematic, a pathologic eosinophilic infiltration of the colon was present in 60–80% of cases [20].

Biology of Eosinophilic Enteritis

The two main laboratory abnormalities present in patients with eosinophilic enteritis are increased number of eosinophils in the blood and increased serum IgE levels [20]. Peripheral blood eosinophilia (eosinophils $>500/\text{mm}^3$) is reported to be present in at least 70–80% of patients with eosinophilic enteritis. This increased number of blood eosinophils is often transient concomitant to flares of the disease and could reach a high level of eosinophilia especially in subserosal disease with ascites. In these particular patients, the analysis of peritoneal liquid samples showed a high level of eosinophils in ascites. The peripheral blood eosinophilia is neither sufficient nor necessary for the diagnosis of eosinophilic enteritis, missing in 1 of 5 patients. Serum IgE levels are abnormally high in over 50% of patients with eosinophilic enteritis without any specificity of the IgE identified. Biological signs of malabsorption (steatorrhea, martial or vitamin deficiency), losing enteropathy (hypoalbuminemia), and intestinal inflammation (increased CRP) may be also present in patients with eosinophilic enteritis [23].

Morphological Characteristics of Eosinophilic Enteritis

Upper gastrointestinal endoscopy and ileocolonoscopy with biopsies are necessary for the diagnosis of eosinophilic enteritis. The endoscopic appearance may be nor-



Fig. 1. Edema of the jejunum. Picture of a small bowel follow-through examination in a patient with a subserosal eosinophilic enteritis showing a thickening wall of the jejunum (arrow).

mal or present nonspecific mucosal abnormalities such as erythema, edema, erosions, ulcers, nodules and stenosis [26]. New endoscopic techniques like wireless capsule endoscopy are useful to explore the entire small intestine and reveal mucosal abnormalities not identified by conventional endoscopy [27]. However, if eosinophilic infiltration is not present in the stomach or proximal small intestine, patients with distal lesions in the small intestine will require enteroscopy in order to perform biopsies and confirm the diagnosis of eosinophilic enteritis [28]. Radiologic exams including abdominal ultrasound, CT scan and MRI are also useful for the diagnosis of eosinophilic enteritis and to characterize the depth of eosinophilic infiltration. Abdominal ultrasound is the investigation of choice to confirm the presence of ascites. Small bowel follow-through was used in the past decade to investigate the small bowel mucosa in patients with eosinophilic enteritis. In these patients, small bowel follow-through could identify wall thickening of the proximal small intestine, stenosis, dilatation of the intestinal lumen and terminal

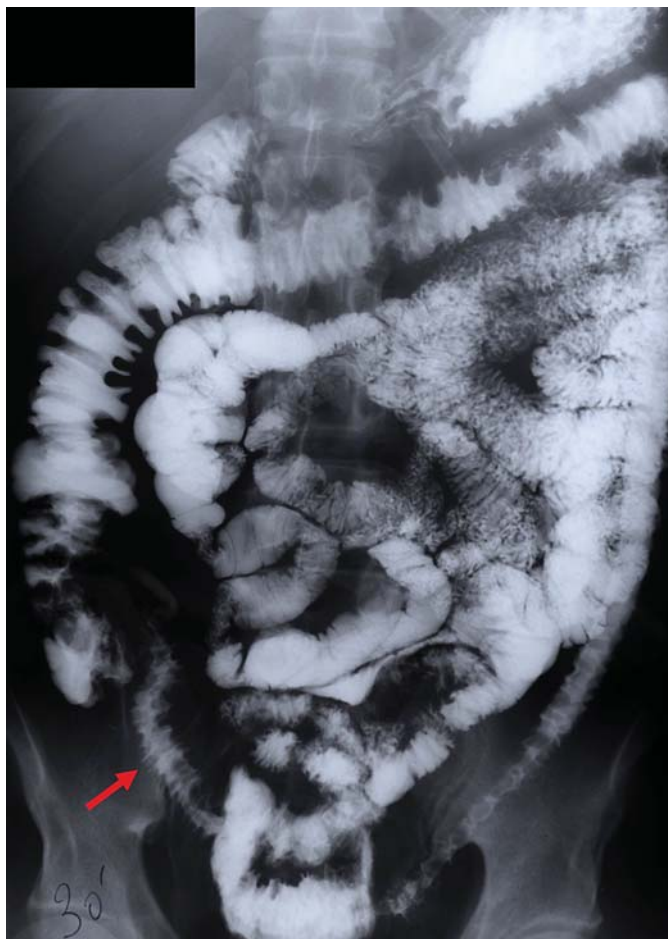


Fig. 2. Terminal ileitis. Picture of a small bowel follow-through examination in a patient with a mucosal eosinophilic gastroenteritis showing an inflamed and ulcerated terminal ileum (arrow).

ulcerated ileitis (fig. 1, 2). Abdominal CT and MRI are useful to evaluate the thickening of the intestinal wall, the extension along the intestine and the presence of ascites (fig. 3).

Diagnosis of Eosinophilic Gastroenteritis

The diagnosis of eosinophilic enteritis may be elusive and is defined as the presence of gastrointestinal symptoms associated with eosinophilic infiltration of the intestinal mucosa and exclusion of secondary causes of intestinal or blood eosinophilia [4]. Gastrointestinal symptoms observed during eosinophilic enteritis are nonspecific, and the key element of the diagnosis is the demonstration of a pathological eosinophilic infiltration

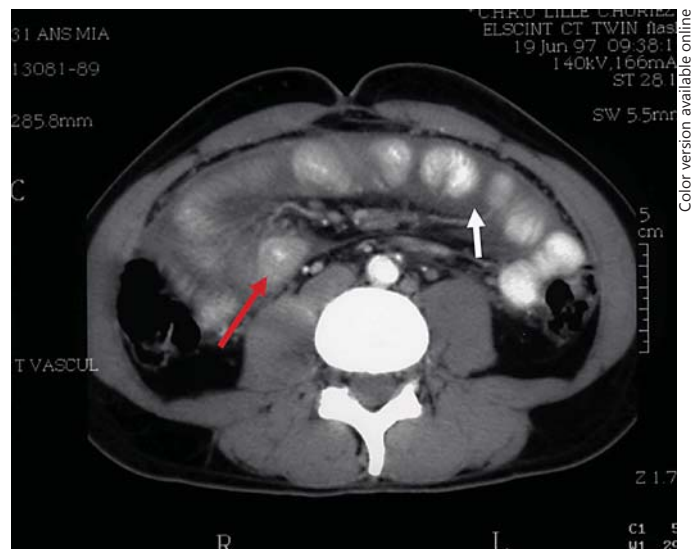


Fig. 3. Diffuse small bowel thickening with ascites. Picture representing a computed tomography slide in a patient with subserosal eosinophilic gastroenteritis. This patient presented diffuse thickening of the small bowel (red arrow; red color refers to the online version only) and ascites (white arrow).

of the mucosa. Eosinophils are usually present in the gut wall except in the esophagus, where they are located in the lamina propria. Their number varies along the digestive tract, and the cutoff to define a pathological infiltration is still debated. In most studies, the threshold of 20 eosinophils per high-power field ($\times 400$) is used for the diagnosis of eosinophilic enteritis [4, 16]. The presence of eosinophils in other layers of the intestinal wall should also be considered as pathologic especially if eosinophils present signs of activation (degranulation). Other findings such as crypt abscesses and architectural abnormalities could increase the likelihood of a pathologic eosinophilic infiltration of the gut. Diagnosis of eosinophilia is based on biopsies during gastrointestinal endoscopy, analysis of ascites fluid in the subserosal forms or analysis of surgical specimens when available.

Pathologic infiltration of the intestinal mucosa with eosinophils is not specific to eosinophilic enteritis, and differential diagnoses should be considered in patients with gastrointestinal symptoms and eosinophilia [29]. Intestinal parasites are one of the most common causes of digestive eosinophilia associated with peripheral blood eosinophilia and must be ruled out by direct stool examination, intestinal biopsies and serological tests. The poor sensitivity of tests used to detect parasites may justify systematic anti-parasitic treatment in patients with

gastrointestinal eosinophilia. Several medications could also be associated with peripheral blood and tissue eosinophilia [30]. Gastrointestinal vasculitis may be accompanied by an increase in eosinophils in the intestinal mucosa [31]. Numerous other gastrointestinal disorders may be associated with eosinophilic infiltration of the intestinal mucosa such as gastroesophageal reflux disease, *Helicobacter pylori* gastritis, celiac disease or inflammatory bowel disease. Finally, it is essential to exclude a hypereosinophilic syndrome which is defined by a peripheral blood eosinophilia >1,500 eosinophils/mm for more than 6 months associated with the involvement of at least one organ [32].

If allergy is suspected to be the cause of eosinophilic enteritis, dietary survey, skin tests and research of specific IgE should be conducted in order to discover specific food allergen. In other cases without allergic history or increased IgE, sequential exclusion of food allergens potentially incriminated is not recommended and mostly not useful to obtain sustained clinical improvement [4].

Treatment of Eosinophilic Enteritis

Treatment of eosinophilic enteritis is not clearly established as there is no randomized controlled trial available in patients with eosinophilic enteritis due to the rarity of the disease. However, it was demonstrated that spontaneous remission may occur in approximately 40% of patients [20]. The main treatment used in patients with eosinophilic enteritis is systemic corticosteroids with a good efficacy in the majority of patients at a loading dose of 20–40 mg/day of prednisone [2, 31]. Budesonide, a corticosteroid that is mostly eliminated by the liver after intestinal absorption, is a therapeutic alternative with fewer systemic side effects. After drug withdrawal, some patients may present a relapse of the disease that requires new treatment with corticosteroids. Steroid-refractory or -dependent cases of eosinophilic enteritis could be treated with immunosuppressive drugs such as azathioprine. Mepolizumab, an anti-IL-5 monoclonal antibody which was previously tested in eosinophilic esophagitis, would be an interesting alternative in patients with a complicated course of eosinophilic enteritis.

Other treatments such as antihistaminic drugs, montelukast and sodium cromoglycate have been used for the treatment of eosinophilic enteritis with conflicting results [31]. Specific diet with exclusion of food allergens previously identified can be useful in selected patients.

Natural History of Eosinophilic Enteritis

The long-term prognosis of eosinophilic enteritis remains unclear. In our case series of patients with eosinophilic enteritis, we were able to describe the natural history of the disease [20]. Indeed, after a median follow-up of 15 years (range 1–27), we identified three distinct clinical courses of eosinophilic enteritis: 18 cases (44%) of which 9 were subserosal forms had a single inaugural flare without recurrence (defined as single flare), 14 (36%) had multiple flares separated by periods of remission (defined as recurring course) and 9 (21%) a chronic form without remission (continuous course). More than 80% of the continuous courses were characterized by a mucosal predominant disease. Subserosal forms evolved in more than 50% of cases a single flare without any recurrence [20]. No myeloproliferative transformation was observed in our cohort of patients with eosinophilic enteritis [20].

Conclusions

Eosinophilic enteritis is responsible for various gastrointestinal symptoms depending on the anatomical form of the disease. The critical finding for eosinophilic enteritis diagnosis is the presence of a pathologic eosinophilic infiltration of the intestinal wall, which should be systematically sought by taking intestinal biopsies in patients with unspecific gastrointestinal symptoms and peripheral blood eosinophilia. The etiology of eosinophilic enteritis is still debated, and the implication of allergy in the pathogenesis remains controversial. Eosinophilic enteritis is often characterized by a benign course without recurrence. However, half of the patients may present a more complex natural history characterized by unpredictable relapses and a chronic course.

Disclosure Statement

The authors declare no conflicts of interest.

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