

Eosinophilic Gastroenteritis and Colitis: a Comprehensive Review

Vikas Uppal¹ · Portia Kreiger² · Erika Kutsch¹

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Abstract Eosinophilic gastrointestinal disorders, including eosinophilic esophagitis, gastroenteritis, and colitis, refer to a spectrum of clinical diseases that present with variable degrees of infiltration of the gastrointestinal tract by eosinophils in the absence of other known causes of tissue eosinophilia. Clinical symptoms and laboratory findings are usually non-specific and may or may not be accompanied by peripheral blood eosinophilia. The extent of eosinophilic infiltration of the gastrointestinal wall varies from mucosal to transmural and serosal involvement. Diagnosis requires presence of gastrointestinal symptoms, demonstration of gastrointestinal eosinophilia by biopsy, and exclusion of other known causes of tissue eosinophilia. Many studies have pointed toward the eosinophil as the major offender; however, the exact functional role of the eosinophil in the pathogenesis of eosinophilic gastrointestinal disorders remains unclear. The roles of T-helper-2 cytokines and other mediators, such as eotaxin-1 and interleukin-5, have gained significant importance in the pathobiology of eosinophilic gastrointestinal disorders. Current understanding of treatment is based on case reports and a few case series, as there is a lack of large prospective studies. Steroids are currently the mainstay of therapy, but the roles of other drugs such as leukotriene inhibitors, mast cell stabilizers, interleukin-5 inhibitors, and anti-immunoglobulin E, along

with other targets in the immune pathway, are currently being explored.

Keywords Eosinophilic gastroenteritis · Eosinophilic colitis · Eosinophil

Introduction

In normal physiologic states, eosinophils are seen in the entire gastrointestinal tract except in the esophagus. Eosinophils are an important part of the innate immune system of the digestive tract, essential to defend against various infectious agents [1]. Eosinophilic infiltration of the gastrointestinal tract can be seen in number of diseases such as parasitic and bacterial infections, inflammatory bowel disease, hypereosinophilic syndrome, connective tissue disorders, myeloproliferative neoplasms, and drug hypersensitivity. Uncommonly, eosinophilic infiltration of the gut occurs in the absence of the aforementioned causes. Although the disorders with such infiltration are collectively referred to as eosinophilic gastrointestinal disorders (EGID) and include eosinophilic esophagitis (EoE), the main focus of this review is on eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC).

The diagnosis of EGID primarily depends upon the demonstration of an increased number of eosinophils in the mucosal biopsy and exclusion of other causes of tissue eosinophilia [2]. However, the pathologic criteria for diagnosis of EGID are not well standardized. For correct diagnosis, a dialogue with the pathologist is essential.

Primary EGID more recently has become well recognized; however, the actual incidence is difficult to estimate due to underdiagnosis. The mucosa of the stomach and small bowel is more commonly involved while colonic involvement is less frequent. Patients present with a variety of non-specific

✉ Erika Kutsch
erika.kutsch@nemours.org

¹ Division of Pediatric Gastroenterology and Nutrition, Nemours/Alfred I. duPont Hospital for Children, 1600 Rockland Rd, Wilmington, DE 19803, USA

² Department of Pathology, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA

symptoms, which can lead to a delay in the diagnosis [3]. Peripheral blood eosinophilia is not universal and may be absent. It has been found that T-helper (Th)-2 cytokines and eosinophilic mediators such as interleukin (IL)-5 and eotaxins play a significant role in the underlying pathobiology [1].

Historical Background

The concept of EGID was first described in 1937 by Kaijser [4]. It was not until 1961 that Ureles et al. were the first to classify EGIDs depending on the presentation: class I with diffuse EGE and class II with well-circumscribed eosinophilic infiltrations forming granulomata, with both further subdivided based on degree of eosinophilic distribution [5].

In 1970, Klein et al. [6] then divided these diseases into three types depending on the depth of eosinophilic infiltration. The classification of Klein et al. proposed three distinct patterns of involvement including predominant mucosal, muscular, and subserosal layer disease [6].

In 1985, Oyaizu et al. presented evidence supporting the hypothesis of an immunoglobulin E (IgE)-induced, mast-cell-mediated mechanism of eosinophilic chemotaxis [7]. In an adult patient with EGE, they found an intense infiltration of eosinophils throughout the entire thickness of the gastric wall. There were also an increased number of IgE-positive plasma cells and mast cells, some of which were degranulated, suggesting an IgE mast-cell-mediated mechanism in EGE development [7].

Fifteen years later, in 1990, Talley et al. evaluated the clinicopathological spectrum of EGE [8]. They described one of the largest cohorts of patients with the diagnosis of EGE, defined by the presence of gastrointestinal symptoms and eosinophilic infiltration of the gut, and divided these patients into three groups based on the Klein classification. They proposed three diagnostic criteria: the presence of gastrointestinal symptoms, biopsies showing eosinophilic infiltration of one or more areas of gastrointestinal tract from esophagus to colon, and characteristic radiologic findings with peripheral eosinophilia and no evidence of parasitic or extraintestinal disease [8].

The same year, Naylor completed a review of 220 case reports of EGE, with particular attention to the clinical presentation and management [9]. He concluded that the stomach was the most commonly affected site, while a third of patients had two or more sites of involvement within the digestive tract at the time of presentation. The most reported presenting symptoms were episodic abdominal pain and diarrhea. Although a history of allergy was present in half of the patients, only 8 % reported aggravation of symptoms following the ingestion of certain foods. The most successful treatment modality was steroid therapy, in which most patients reported rapid clinical improvement [9].

In 1993, Lee et al. published the first longitudinal study of eight adult patients with EGE [10]. Initial presenting symptoms were similar to those previously described in the literature. These authors also remarked on the relapsing nature of the disease as four of the eight patients needed chronic low-dose steroid therapy to maintain remission [10].

In 1996, Desreumaux et al. evaluated the mechanism for the intestinal recruitment of eosinophils to the digestive tract in ten patients with EGE [11]. They examined the presence of immunoreactivity for granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5 within cells in the mucosa of duodenum and colon. They found that the presence of these cytokines was associated with a dense eosinophil infiltration of the lamina propria, and they concluded that this infiltration may be linked to the local production of IL-3, GM-CSF, and IL-5 within eosinophil granules [11].

Later that year, Bischoff described the role of mast cells and eosinophil granulocytes in the pathogenesis of EGID in a comprehensive review [12]. He summarized that the immediate phase of allergic reactions is dependent on mast cell activation through the high-affinity IgE receptor. The late-phase reaction involves not only mast cells, but also allergen-reactive Th-2 lymphocytes producing cytokines (IL-3, IL-5, GM-CSF), monocytes generating chemokines (interleukin-8 [IL-8], monocyte chemoattractant protein [MCP] 1 and 3), and granulocytes. Eosinophil and basophil granulocytes then accumulate at sites of allergic inflammation and release inflammatory mediators inducing tissue destruction and organ dysfunction [12].

Definition and Epidemiology

EGE is an uncommon, chronic condition of the digestive tract, characterized by eosinophilic infiltration of the gastrointestinal wall, typically involving the stomach, small intestines, and, less commonly, the colon [13]. It may or may not be accompanied by peripheral eosinophilia [14]. The exact incidence of disease is unknown because many cases are not properly diagnosed or reported. The estimated incidence of EGE remains relatively rare with 1–20 cases per 100,000 patients [15]. EC is the rarest reported form of EGID although there has been a rise in cases over the last decade, possibly due to increased recognition of it as a distinct disease entity [3]. Although cases have been reported from infancy to adulthood, the peak incidence of presentation is typically during the third to fifth decade of life [10, 16, 17]. EGIDs have been described in both sexes, with a slight male predominance of 3:2 [17]. The diagnosis is most commonly described in the Caucasian population, but there are reports documenting occurrence in all races and ethnic backgrounds [14, 18–20]. Most of these patients, up to 70 %, report a personal or family history of

other concurrent atopic disorders including asthma, eczema, or hay fever [21].

Pathophysiology

In contrast to the esophagus, the stomach and small bowel often demonstrate easily detectable eosinophils under physiological conditions. In a subset of primary EGE patients, elevated total IgE and food-specific IgE have been detected [22]. Most patients have positive skin allergen test to a variety of food substances without any anaphylactic reaction. The immune response to various food allergens in the setting of EGE is considered to be a delayed type of hypersensitivity reaction. This concept has been proven in mice after experimental induction of EGE by administration of oral allergens. The mice subsequently showed features of delayed hypersensitivity in the gastrointestinal tract such as gastromegaly, delayed gastric emptying, and weight loss. It is noteworthy to mention that all of these responses are strongly dependent on the chemokine eotaxin-1 [23].

Eosinophils are the key cells implicated in the pathogenesis of EGE and EC. Even though found in peripheral blood circulation, eosinophils are predominantly tissue-dwelling cells. The cell morphology is characterized by distinctive cytoplasmic granules that stain with acidic dyes, such as eosin. In the bone marrow, eosinophils undergo maturation and differentiation under the effect of several transcription factors including GATA-1, GATA-2, and C/EBP [24–26]. These transcription factors interact with the eosinophil growth factors IL-3, IL-5, and GM-CSF. Eosinophils spend approximately 8 days in the bone marrow and then relocate to the peripheral circulation where they comprise roughly 1 to 3 % of all white cells. After a brief half-life of 8 to 12 h, they start trafficking to the tissues of the digestive tract [27].

IL-5 is a key mediator in eosinophil activation and is required for expansion of eosinophils and their release from bone marrow [28]. The overproduction of IL-5 in murine models has been reported to result in profound blood eosinophilia [29]. On the other hand, deletion of the IL-5 gene causes a marked decrease in circulating eosinophils in the gastrointestinal tract and lungs after an allergen challenge [30].

The translocation of eosinophils from blood to tissues encompasses additional steps such as adhesion and diapedesis, which are primarily regulated by the chemokine receptor family eotaxin-1, eotaxin-2, and b-3 [31]. Eotaxin-1 plays a key role in eosinophil accumulation and chemotaxis in the gut [23]. Eotaxin-1-deficient mice have been reported to show impaired eosinophil trafficking to the digestive tract [23].

Eosinophils are recruited in response to several stimuli including non-specific tissue injury, allergens, and infections including parasites. Upon activation, eosinophils degranulate and secrete several cytokines. The eosinophil granules contain

four major cationic proteins including eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and major basic protein (MBP). MBP, EPO, and ECP have cytotoxic effects on the epithelium. ECP and EDN have an additional ribonuclease activity. ECP has the ability to insert voltage-insensitive and ion-non-selective pores into target cells, and these pores facilitate entry of other toxic molecules [32]. The MBP can directly induce degranulation of mast cells and basophils. The MBP can also cause dysfunction of vagal muscarinic receptors (M2) and an increase in smooth muscle reactivity [33]. The other mediators secreted by eosinophils include leukotrienes, which are potent smooth muscle constrictors. Leukotrienes promote vascular permeability and mucus secretion [34]. Eosinophils also express a wide range of other immune mediators that potentiate an inflammatory response: IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, GM-CSF, transforming growth factor alpha and beta (TGF- α/β), tumor necrosis factor (TNF), and eotaxins. Eosinophil-derived TGF- β is reportedly associated with epithelial growth, tissue remodeling, and fibrosis. EPO can generate a large amount of toxic hydrogen peroxide and halide acids, which, in turn, cause tissue damage [1].

Many studies have demonstrated evidence of extracellular deposition of MBP and ECP in the small intestinal mucosa of patients with EGID [8, 35, 36]. Duodenal biopsies in patients with EGE have demonstrated ultrastructural changes in eosinophils that indicate degranulation and mediator release [35]. Microscopic examination of stool samples from patients with EGID frequently shows Charcot-Leyden crystals and remnants of eosinophilic degranulation [37].

EC is rare and affects infants as well as adults. It is possible that EC of infancy is an early manifestation of protein-induced enteropathy [38]. Some studies have shown evidence of mast cell accumulation and degranulation in EC supporting the role of IgE in its pathogenesis [39, 40]. In contrast, EC in adults appears to be non-IgE-mediated [1]. It has been suggested that T-cells play a key role in the pathogenesis of this disease [41].

Clinical Presentation

Symptoms of EGID are not disease-specific and can be seen in various other gastrointestinal disorders, often leading to extensive testing and delay in diagnosis. Patients most commonly report abdominal pain but may also have nausea, vomiting, poor appetite, weight loss, and diarrhea at the time of diagnosis [2]. As discussed previously, disease presentation can occur at any age but most often occurs between the third and fifth decades of life. Pediatric case reports are rare. In a small case series of 14 pediatric patients, the median age at time of diagnosis was 8.3 years and the median duration from onset of symptoms to diagnosis was 3 months. Initial symptoms included abdominal pain and recurrent vomiting. Half of the

patients presented with gross or occult hematochezia, and 36 % of patients had significant anemia with a hemoglobin <8 mg/dL [42]. Both pediatric and adult patients with EGE often exhibit prior or concurrent history of atopy, including asthma, allergic rhinitis, and elevated serum IgE [42, 43].

Patients with EGE may present with varying clinical symptoms based on location and the depth of eosinophilic infiltration of the bowel wall. The most commonly reported sites of involvement include the stomach and small intestine; however, the esophagus, large intestine, and rectum may also be involved to various degrees [8–10, 44]. The classification previously described by Klein et al. [6] divides EGE into three distinct types: mucosal, muscular, and subserosal.

Mucosal

The mucosal subtype is the most commonly reported form of EGE possibly due to the ease of obtaining mucosal tissue samples during routine endoscopy [45]. Patients often present with vague, non-specific symptoms of abdominal pain, nausea, diarrhea, and vomiting which may mimic other gastrointestinal diseases. Some patients may present with more severe symptoms related to blood loss in stools, iron deficiency anemia, malabsorption, or a protein-losing enteropathy [46–48]. All parts of the digestive tract may be affected, esophagus to rectum, even eosinophilic infiltration of the bile ducts has been reported previously [8, 49]. In one adult study, 52 of 59 patients had mucosal involvement, compared with three with muscular and four with subserosal disease. This study demonstrated a predominance of mucosal disease, confirming a greater shift away from muscular disease contrary to results reported previously by other investigators [43].

Muscular

The muscular subtype, the second most commonly reported form, is characterized by infiltration of eosinophils predominantly in the muscle layer, causing bowel wall thickening and, in turn, symptoms of intestinal obstruction [50]. Gastric outlet obstruction, caused by distal stomach and pyloric submucosal infiltration, has been reported in the adult population. In infants, it may mimic pyloric stenosis [49–51]. More distal intestinal obstruction, although rare, has been described in the literature and may occur in the ileum [50] and jejunum [52]. In patients with EC affecting the left colon, obstructive colo-colonic intussusception has been reported [53].

Serosal

The serosal subtype is the most unusual and least reported form of EGE. Patients typically present with isolated abdominal ascites or ascites along with symptoms more characteristic

of the mucosal or muscular forms of EGE [6]. Eosinophilic ascites can be accompanied by eosinophilic pleural effusions [37]. In contrast to the other forms of EGE, eosinophilic ascites is more commonly reported in middle-aged women [54] but has also been reported in early infancy [55]. The hallmark of this subtype is marked eosinophilia in the ascitic fluid [6]. Serosal EGE often has a better response to steroids [56].

The presentation of EC, as with EGE, tends to depend on which intestinal layer is most affected by the eosinophilic infiltration. Mucosal disease typically leads to malabsorption, diarrhea, and protein-losing enteropathy. Transmural disease, reported to a lesser extent, presents with colonic wall thickening and intestinal obstruction [3, 56, 57]. Patients with EC may also demonstrate perianal disease [58], visceral neuropathy, and chronic intestinal pseudo-obstruction [59], cecal volvulus [60], and appendicitis [61]. EC may have similar features to that of colon carcinoma on barium enema, and care must be taken with radiographic interpretation of this test, especially in the elderly population [62].

Eosinophilic Proctocolitis

Eosinophilic proctocolitis of infancy occurs in infants who are breast-fed or receiving a cow's milk or soy-milk-based formula. Presenting symptoms typically occur by 2 months of age and include chronic diarrhea containing blood and mucus. Visual changes during colonoscopy are variable but may include patchy, localized erythema, edema, and, occasionally, lymphoid nodules. Histology may demonstrate eosinophilic and plasma cell infiltration of the lamina propria [16]. Both clinical symptoms and histologic changes tend to improve on an appropriate exclusion diet or elemental formula. These children are often able to tolerate cow's milk or soy protein once they reach toddlerhood [63].

Diagnostic Evaluation

There is no single laboratory test or procedure that is diagnostic of EGE. Maintaining a high index of clinical suspicion is important [64]. Criteria essential for making the diagnosis of EGE include the presence of gastrointestinal symptoms, eosinophilic infiltration of the digestive tract, and exclusion of other causes of intestinal eosinophilia.

Laboratory Findings

After completing a thorough history and physical examination, which focuses on specific food and environmental allergic triggers and atopic features such as asthma, rhinitis, and eczema, obtaining a complete blood count for evaluation of

peripheral eosinophilia can be helpful. Peripheral eosinophilia (absolute eosinophil count [AEC] ≥ 600 cells/ μL) is indicative of an underlying eosinophilic disorder. The degree of peripheral eosinophilia, in the absence of treatment, can be divided into mild (AEC 600–1500 cells/ μL), moderate (AEC 1500–5000 cells/ μL), or severe (AEC >5000 cells/ μL) [65]. Although not present in every patient, blood peripheral eosinophilia can be seen in 20 to 80 % of cases of EGE, with higher levels in patients with a serosal predominant pattern [66]. Further evaluation, including elevated erythrocyte sedimentation rate, iron deficiency anemia, elevated IgE level, and low serum albumin, may also support the diagnosis. Stool examination to rule out parasitic infections should also be performed. Fecal protein loss may be assessed by obtaining a stool α -1 antitrypsin clearance. Mild to moderate steatorrhea has also been described and can be measured with quantitative fecal fat testing.

Allergy Testing

Evaluation of atopy, including skin prick testing, radioallergosorbent (RAST), and patch testing, is often utilized to assess specific food and environmental allergies that may trigger the onset of symptoms, contributing to the pathogenesis of disease. However, the role of allergy testing often comes into question as the development of EGID likely results from a combined IgE-mediated and non-IgE-mediated Th-2 delayed hypersensitive response by gastrointestinal epithelium to exogenous antigen exposure. As allergy testing predominately evaluates for IgE-mediated responses, its usefulness for this disease may be limited [67]. Allergen-specific IgE and skin prick tests, when positive, indicate a sensitized state. However, the clinical utility of the positive results remains controversial [67]. It is important to keep in mind that individuals can become tolerant to food allergens. According to the recent guidelines for management of food allergy in USA, food-specific IgE and skin prick can be used to identify the specific food allergens in EoE but alone are insufficient for diagnosis [68].

Radiographic Evaluation

The usefulness of imaging in the diagnosis of EGE is limited as the findings are variable, non-specific, and are often not found in most patients. Ultrasonography is a quick, inexpensive, and non-invasive way to detect the presence of bowel wall thickening, ascites, and peritoneal nodules that may be suggestive of EGE disease in the proper clinical setting and may prevent unnecessary invasive exams or abdominal surgery. It may also be used in the follow-up of patients to monitor response to therapy [69].

Computerized tomography (CT) scan may demonstrate nodular, irregular folds, and thickening of the stomach and

small intestines [70]. In pediatric patients with EC, colonic wall thickening, predominantly cecal or mild to moderate terminal ileal thickening, may be seen on CT scan, often mimicking the findings of Crohn's disease [71].

Barium contrast studies may show variable degrees of antral stenosis and mucosal irregularity of the stomach along with thickened mucosal folds of the small intestine due to edema [17]. In patients presenting with antral eosinophilic gastritis, a string sign may be seen as a sign of gastric outlet obstruction [51]. A few studies have reported the usefulness of Tc-99m hexamethylpropyleneamine oxime (HMPAO) scintigraphy scanning in detection of active eosinophilic inflammation, extent of disease, and assessment of the response to treatment [72, 73].

Endoscopy

The endoscopic findings of EGE and EC may appear normal or may demonstrate changes like non-specific gastritis or colitis [16]. However, findings of mucosal erythema, friability, and fine granularity in the stomach have been reported [74]. Ulcerated mucosa (Fig. 1), thickening of gastric mucosal folds and mucosal nodules (Fig. 2), or whitish specks (Fig. 3) can also be seen.

Pathology

The diagnosis of EGE and EC can be confirmed on histopathological examination of gastric, duodenal, and colonic biopsies (Figs. 4 and 5). Examination of eosinophils throughout the gastrointestinal tract of conventional healthy mice

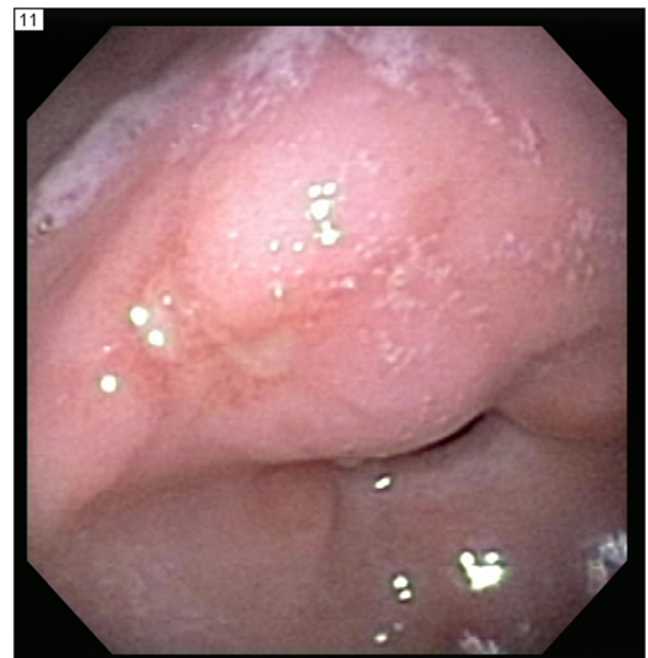


Fig. 1 Antral ulcer in an 18-year-old patient with eosinophilic gastritis

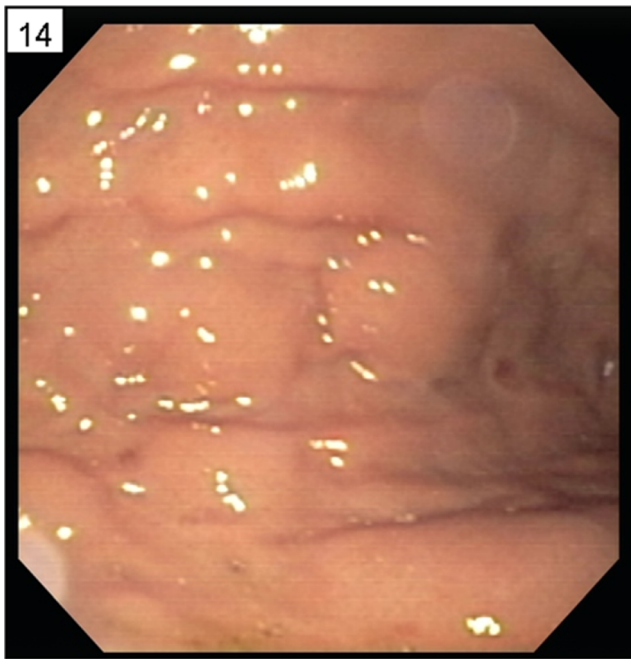


Fig. 2 Submucosal nodules and gastric fold thickening in a 3-year-old patient with eosinophilic gastritis

revealed that eosinophils are normally present in the lamina propria of the stomach, small intestine, cecum, and colon [75]. Similar findings have been described in humans [76]. The cecum and appendix have been noted to have the highest concentration of eosinophils (up to 30 eosinophils/high-power field) with lower counts in the stomach and distal large intestine, with more than half of the samples examined having eosinophil counts of >20 eosinophils/high-power field from at least one site within the digestive tract [76]. The relative rarity of the disease limits well-designed studies and accounts for a general lack of consensus on histological features. The most

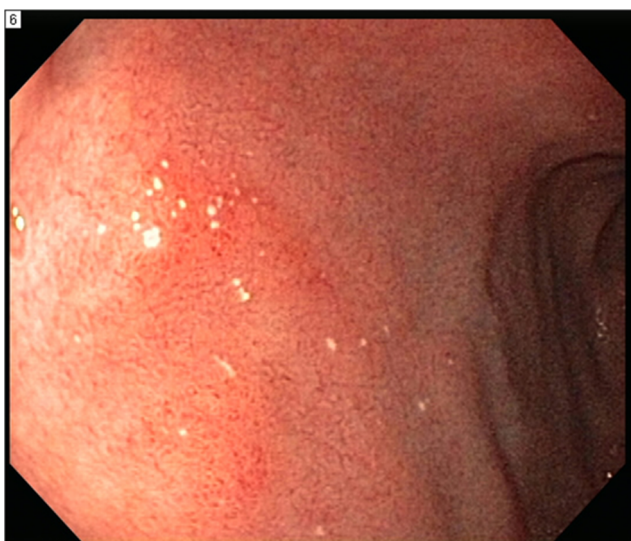


Fig. 3 White plaques in the duodenal bulb in a 16-year-old patient with eosinophilic enteritis

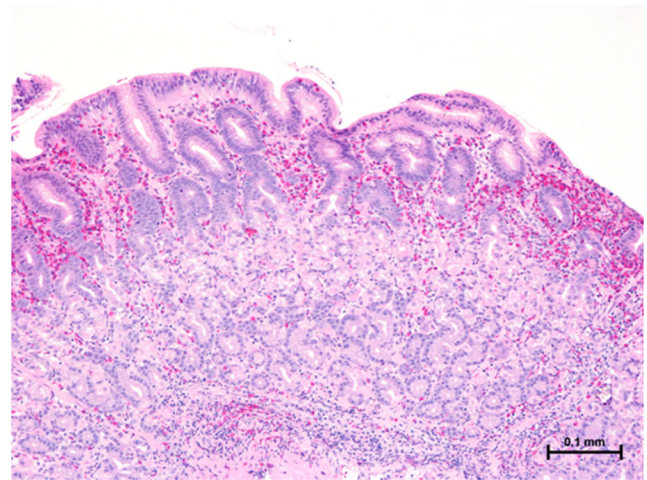


Fig. 4 Fundic-type gastric mucosa with an increased number of lamina propria eosinophils, most marked within the superficial lamina propria, with occasional eosinophils infiltrating the overlying superficial epithelium, consistent with gastric eosinophilia [H&E, original magnification $\times 100$]

accepted definition is an eosinophil count exceeding more than 20 per high-power field on microscopic examination [8, 14, 16]. Biopsies demonstrating increased eosinophil inflammation may reveal extracellular deposition of eosinophil granule constituents, containing MBP and ECP, both of which can be detected immunohistochemically at increased levels [1, 77]. The distribution of eosinophils is often patchy and may be present in normal-appearing mucosa. Thus, obtaining multiple biopsy samples throughout the digestive tract, including visually normal areas, may be helpful in establishing the diagnosis [8, 78]. The evaluation of muscular or serosal EGE is often difficult but laparotomy [50], capsule endoscopy, and balloon enteroscopy [79] have been useful in diagnostic confirmation.

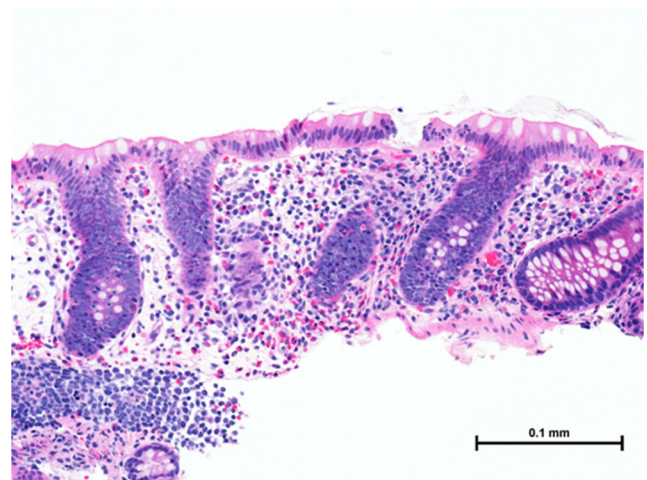


Fig. 5 Colonic mucosa with an increased number of eosinophils within the lamina propria as well as occasional eosinophils infiltrating crypts, consistent with colonic eosinophilia [H&E, original magnification $\times 200$]

Differential Diagnosis

Other conditions presenting with gastrointestinal symptoms having associated peripheral eosinophilia should be differentiated from EGE and EC. EGIDs can be categorized into two main types: primary and secondary (Table 1). Primary EGE is usually idiopathic even though an allergic mechanism may be identified. The diseases associated with secondary EGE include hypereosinophilic syndrome, Churg-Strauss syndrome, celiac disease, inflammatory bowel disease, polyarteritis nodosa, other connective tissue disorders, infections, and drug hypersensitivity. These conditions typically can be differentiated with the use of careful history taking, laboratory testing, and histologic examination of endoscopic biopsies.

Intestinal parasites such as *Enterobius vermicularis* (pinworms), *Ancylostoma caninum* (hookworms), *Ascaris*, *Anisakis*, *Eustoma rotundatum*, *Trichuris*, and *Schistosoma* can be associated with tissue and peripheral eosinophilia [80–87]. Infection with *Toxocara canis* has resulted in eosinophilic ascites [88]. Case reports have described patients with findings of EC in which *Strongyloides stercoralis* was found to be the causative organism [89, 90]. The diagnosis of intestinal parasites should be excluded with the use of stool ova and parasite evaluation, serology, duodenal aspirates, and endoscopic biopsies. Diagnostic paracentesis should be performed in patients presenting with suspected eosinophilic ascites.

Although EGE in *Helicobacter pylori*-positive patients is rare, there are cases reporting the efficacy of *H. pylori* eradication using traditional therapy in the treatment of EGE [91, 92]. Careful histological examination of gastric biopsies with silver staining would aid in ruling out *H. pylori* infection.

Patients with inflammatory bowel disease may present with peripheral and intestinal eosinophilia, but it is usually differentiated from EGID by the lack of florid eosinophils on biopsies and other clinicopathologic findings typically associated with inflammatory bowel disease [93].

Table 1 Differential diagnosis of eosinophilic gastroenteritis

Primary
1. Idiopathic
2. Allergic
Secondary
1. Hypereosinophilic syndrome
2. Parasitic infections
3. Inflammatory bowel disease
4. <i>Helicobacter pylori</i>
5. Churg-Strauss syndrome
6. Polyarteritis nodosa and other connective tissue disorders
7. Celiac disease
8. Drugs (gold compounds, rifampicin, clofazimine, gemfibrozil, azathioprine, enalapril, naproxen, interferon, tacrolimus, and others)

Hypereosinophilia syndrome is a rare, idiopathic condition. It is associated with marked peripheral eosinophilia often exceeding 1500 cells/ μ L that persists for greater than 6 months, along with the presence of organ damage or dysfunction related to eosinophilic infiltration and release of mediators. The most common presenting manifestations of hypereosinophilia syndrome were dermatologic, pulmonary, and gastrointestinal. Cardiac and neurologic complications did occur but were relatively uncommon at the initial presentation [94].

Vasculitic disorders, such as Churg-Strauss syndrome and polyarteritis nodosa, are characterized by an eosinophilic infiltrate of the small blood vessels in the digestive tract and peripheral eosinophilia, along with elevated markers of inflammation and autoantibodies [17]. Several of the connective tissue disorders, especially scleroderma and dermatomyositis, are also associated with symptomatic involvement of the digestive tract. These disorders often present with episodic peripheral eosinophilia and a band-like infiltrate of the lamina propria with eosinophils and mast cells [95].

A number of medications have been associated with gastrointestinal eosinophilia and are thought to be secondary to drug allergy. Some of these medications include carbamazepine [96], gold compounds [97], rifampicin [98], naproxen and other non-steroidal anti-inflammatory drugs [99, 100], interferon [101], azathioprine [102], gemfibrozil [103], clofazimine [104], and enalapril [105]. Saeed et al. reported three cases of EC in liver transplant recipients, maintained on tacrolimus [106]. These patients also had high serum IgE levels, peripheral eosinophilia, and IgE-positive RAST test for milk proteins. The EC appeared to be mediated by food allergies as each patient had symptomatic improvement following reduction in immunosuppression and an appropriately restricted diet [106].

Treatment

There has been no definitive consensus regarding the treatment of patients with EGID, likely due to the lack of large-scale, prospective controlled studies. Thus, treatment is empiric and based on the severity of the clinical manifestations.

Dietary Elimination

The uses of elimination and elemental diets have been shown to improve clinical symptoms and reduce mucosal eosinophils in patients with EoE [107]. Thus, a similar treatment strategy has also been utilized in the treatment of EGE and EC. Most of the evidence supporting the use of dietary restriction in patients with EGE and EC is from retrospective studies and small case reports. Successful treatment with dietary therapy may also be influenced by distribution of eosinophilic infiltration, age of the patient, and ability to comply with dietary

restriction. Allergy testing should be considered for patients with EGID, including skin prick and RAST testing, as selective food elimination may be helpful in some patients. However, although many individuals generate food-specific IgE antibodies detected by allergy testing, they may have no reaction following ingestion [67]. Furthermore, the offending foods are sometimes difficult to determine, especially in older children, as food-specific IgE and a positive prick test may only be found in half of the patients tested due to non-IgE-mediated food allergies [108]. As eliminating the intake of foods found on skin prick or RAST testing has variable effects, symptomatic and histologic remission has been described with the use of exclusively elemental diets and may be used as a steroid-sparing option [51, 109]. In six pediatric patients with allergic EGE with associated anemia and hypoalbuminemia caused by protein-losing enteropathy, Chehade et al. demonstrated that treatment with a diet composed exclusively of an amino acid-based formula was more effective than elimination diets and resulted in rapid resolution of clinical symptoms, hypoalbuminemia, and anemia in less than 4 weeks in all patients [110]. Unfortunately, the long-term efficacy of elemental diets has not been studied, may be complicated by micronutrient deficiencies such as selenium and essential fatty acids, and can be costly. Compliance is often an issue. The efficacy of a six-food elimination diet (milk, soy, eggs, wheat, peanuts/tree nuts, and shellfish/fish) in a pediatric patient with EG was recently reported, but the results may be confounded as this patient also received treatment with antihistamines and suplatast tosilate [111]. Another case report demonstrated symptomatic improvement and a decrease in the ECP level in an adult patient after empiric removal of cow's milk from the diet despite having a negative allergic evaluation [112]. Patient with allergic enteritis with clinical manifestations of allergy (asthma, eczema, allergic rhinitis), elevated IgE levels, and peripheral eosinophilia may respond to dietary modifications, but the response is not universal [113].

Unfortunately, a commonly encountered issue of dietary restrictive therapy is recurrence of symptoms with the reintroduction of food.

Steroids

Systemic and topical corticosteroids remain the mainstay of therapy for EGID [114] and are typically reserved for those with severe disease presentation or for those in whom dietary measures are not successful or feasible. Steroids have been shown to be effective via inhibition of eosinophilic growth factors IL-3, IL-5, and GM-CSF [115]. EGIDs are exquisitely sensitive to corticosteroid therapy, and a lack of an initial response to corticosteroids should prompt a reexamination of the diagnosis [116]. There are a number of studies demonstrating rapid and sustained remission while on steroids [8–10]. Various treatment strategies have been reported, but

most patients will benefit from an initial course of 2 to 6 weeks, with daily dosages ranging from 20 to 40 mg of prednisone (1–2 mg/kg per day), with tapering regimens over a few weeks to months. The treatment course is variable; some patients have no reoccurrence [6, 10], whereas most patients will relapse with steroid withdrawal or when treatment has been discontinued. These patients may require long-term, low-dose maintenance therapy or periodic corticosteroid bursts [13, 117]. However, long-term steroid use has been associated with growth suppression, bone abnormalities such as osteopenia, mood disturbances, and adrenal axis suppression [118] and should be used with caution.

An alternative to systemic steroids is budesonide, a corticosteroid that acts locally, with an efficacy similar to that of prednisone. Budesonide is a synthetic steroid with high topical glucocorticoid activity and low systemic bioavailability due to its high first-pass hepatic metabolism, minimizing systemic side effects [119]. In one case report, a patient diagnosed with eosinophilic enterocolitis who was losing protein from cecum and terminal ileum (detected by technetium-99m-labeled albumin scintigraphy) was successfully treated with budesonide. Treatment with budesonide resulted in improvement in clinical condition, decreased tissue eosinophilia, and protein loss in cecum and terminal ileum [120]. There are several cases reporting successful transition from systemic corticosteroid to budesonide in EGID [120]. The use of enteric-coated budesonide in treatment of eosinophilic enterocolitis has been described [121]. Others have used non-enterically coated preparations in EGE involving the stomach and small intestine [122].

Other treatment modalities are primarily used as steroid-sparing agents and include cromolyn sodium (mast cell stabilizer), ketotifen (inhibits secretion of mast cell mediators such as histamine), montelukast (competitive leukotriene receptor antagonist), and suplatast tosilate (selective Th-2, cytokine IL-4, and IL-5 inhibitor).

Cromolyn

Cromolyn sodium is a mast cell stabilizer, and it has been used with some success in patients with EGE with mucosal and subserosal disease, alone or in combination with steroids [14, 123]. Cromolyn acts locally on the gastrointestinal mucosa with little systemic absorption [124]. The recommended oral dose varies from 100 to 300 mg per dose four times daily in adult patients.

Ketotifen and Suplatast

Ketotifen has a mast-cell-membrane-stabilizing and antihistaminic effect. It is administered in dosages of 2–4 mg per day. Melamed et al. [125] noticed improvement in symptoms, tissue clearing of eosinophils, and a decrease in IgE levels after

12 months of treatment with ketotifen in six patients with EGE and elevated IgE levels. IgE levels decreased after 4 to 6 months of therapy [125]. Suplatast is an anti-Th-2 medication that inhibits the expression of Th-2 cytokines. There are a few cases reporting improvement in EGE with the use of suplatast [126, 127]; larger trials have yet to be completed. Neither medication is available in the USA.

Montelukast

Montelukast is a selective, competitive leukotriene receptor antagonist. It blocks Cys-LT 1 receptor leading to blockade of actions of leukotriene D₄, which causes increased vascular permeability, smooth muscle contraction, and chemotaxis [21]. Leukotrienes also enhance proliferation of bone marrow eosinophil and basophil precursors [21]. It has been used in combination with steroids as a steroid-sparing agent. One study showed that four of 14 patients treated with montelukast alone did not have relapse [42]. Others have reported symptom relief in patients with dyspepsia due to duodenal eosinophilia in response to montelukast [128]. In contrast, montelukast had no effect on tissue eosinophils or symptoms in a patient with severe, long-standing EGE complicated by an esophageal stricture even though there was an improvement in peripheral eosinophilia [129].

Biologicals

Therapy targeting specific pathways of the inflammatory cascade is currently under investigation and may offer possible treatment options in patients with EGE and EC. As there are similarities in the pathogenesis of EGE and EC with EoE, biologic medications undergoing clinical trials for the treatment of EoE are briefly discussed as potential therapeutic agents for EGE and EC.

Omalizumab is a humanized therapeutic anti-IgE monoclonal antibody that reduces free IgE levels and has been found to be an effective treatment for allergic asthma and seasonal allergic rhinitis. Omalizumab binds to IgE and prevents it binding to Fc-epsilon-RI, leading to inhibition of mast cell and basophil activation [130]. Foroughi et al. [131] showed that although omalizumab significantly decreased serum-free IgE levels, improvements in eosinophil-associated gastrointestinal disorder symptoms did not correlate with changes in peripheral or tissue eosinophilia. Also, changes in tissue eosinophil count did not correlate with changes in blood AEC [131]. This suggests that blocking IgE alone may not be effective EGE and EC management.

Reslizumab and mepolizumab are two humanized anti-IL-5 antibodies that have shown efficacy in clinical trials for asthma and hypereosinophilic syndrome. Anti-IL-5 antibodies target eosinophils by binding to IL-5, interfering with its ligation to IL-5R α expressed on the eosinophil membrane [132].

In a double-blind, randomized, placebo-controlled trial of reslizumab in children and adolescents with EoE, reslizumab significantly reduced intraepithelial esophageal eosinophil counts in children and adolescents with EoE. Although there was symptomatic improvement observed in all treatment groups, this was not associated with changes in esophageal eosinophil counts [107]. Another small study examined the effects of a single dose of reslizumab in eight adult patients with either hypereosinophilic syndrome or EGE refractory or intolerant of conventional therapy. Despite improvement of eosinophilia and clinical symptoms in six of eight patients for as long as 12 weeks, eosinophil counts subsequently rose above baseline levels, accompanied by an exacerbation of symptoms [133]. Mepolizumab has been studied in patients with EoE, and in a small randomized, placebo-controlled, double-blind study in the treatment of adults with EoE, it resulted in a 67 % reduction in tissue eosinophils compared with a 25 % reduction in the subjects treated with placebo. Peripheral blood eosinophils counts also decreased in subjects treated with mepolizumab compared with placebo. Half of the patients treated with mepolizumab also reported improvement of their dysphagia after treatment [134]. Larger randomized, controlled trials are needed to further clarify the efficacy and safety of this drug class in patients with EGE and EC.

The use of anti-tumor necrosis factor (TNF)- α in the treatment of severe adult EoE has been explored. Infliximab, a chimeric immunoglobulin-G1 antibody, inhibits TNF- α [135]. Blocking TNF- α activity is currently approved in the treatment of several chronic inflammatory diseases, including Crohn's disease and rheumatoid arthritis. In a small study of three male patients with severe, steroid-dependent EoE, each participant received two infusions of infliximab (5 mg/kg), at weeks 0 and 2. Although there was mild symptomatic improvement in two patients, one had worsening symptoms, and none had endoscopic improvement after infliximab treatment. This study suggests that infliximab, with standard induction dosing, is not able to induce endoscopic remission of EoE, nor does it markedly reduce symptoms related to EoE disease [135].

OC000459 is a selective chemoattractant receptor-homologous molecule on Th-2 cell (CRTH2) antagonist that has been studied in adult patients in EoE [136]. This CRTH2 is a prostaglandin D₂ (PGD₂) receptor, expressed by Th-2 cells, eosinophils, and basophils, that mediates eosinophil chemotaxis and recruitment. In a randomized, double-blind, placebo-controlled trial, 26 adult patients with active EoE, dependent on or resistant to corticosteroids, were treated either with OC000459 100 mg or placebo twice daily. After 8 weeks of treatment, there was a slight reduction in the baseline eosinophil count in those receiving the study drug. However, there was no significant improvement in the endoscopic appearance after treatment [136].

Potential Future Treatment Targets

Based on the current understanding of the pathophysiology of EGID, there are several pathways that are under current investigation for potential future treatment options of eosinophil-related diseases. For example, sialic-acid-binding immunoglobulin-like lectin (siglec-8) is expressed on human eosinophils, where its ligation with ligand-coated polymers or anti-siglec-8 antibodies induces apoptosis [137]. Studies in human tissue from patients with eosinophilic disease demonstrate significant eosinophil cytotoxicity, which might be due to regulated necrosis. The ability to impede necrosis or redirect cell death from necrosis to apoptosis may lead to improved therapies in patients with eosinophilic conditions [137]. Ben Baruch-Morgenstern et al. recently demonstrated that IL-5 activity in eosinophils was regulated by paired immunoglobulin-like receptors A and B, which may offer a way of regulating IL-5-induced expansion of the eosinophil [138]. CC-chemokine receptor 3 (CCR3) is an eotaxin receptor known to be involved in eosinophil chemotaxis. Komai et al. reported that CCR3 antagonism not only prevents the infiltration of eosinophils into the airways but also prevents the development of allergen-induced subepithelial and peribronchial fibrosis in mouse models [139]. IL-4 and IL-13 are two cytokines produced by activated CD4⁺ T cells and are important in the development of allergic responses [140]. IL-4 promotes the differentiation and proliferation of Th-2 cells and the synthesis of IgE, whereas IL-13 mediates airway hyperresponsiveness and mucus hypersecretion. Both cytokines signal through the type II IL-4R α polypeptide [140]. Pitrakinra, currently under clinical development, is an IL-4 variant or mutein, which binds to the IL-4R α subunit, thus preventing the binding and inflammation induced by IL-4 and IL-13 [141]. This drug is undergoing evaluation in patients primarily with asthma and eczema but may have a role in EGID treatment, in which inflammation is also partially Th-2-driven. Benralizumab is a humanized recombinant IgG1k isotype monoclonal antibody. It binds with high affinity to the α -chain of the IL-5 receptor that is expressed on eosinophils and basophils, in turn, inhibiting IL-5-mediated receptor activation [142]. It is currently in trials for patients with asthma but may have a future role in EGID therapy.

Summary/Conclusion

Primary EGID are rare disorders that have been increasingly recognized over the past decade, and the true incidence is difficult to estimate due to underreporting of many cases. Recent studies have highlighted the role of Th-2 cytokines and eotaxins in the pathophysiology. The pathophysiology and natural history of EC vary with the age of the patient. Clinical and laboratory findings are often non-specific. Depending upon the

site and depth of involvement, presenting symptoms vary from nausea, vomiting, and abdominal pain, to some patients developing protein-losing enteropathy, ascites, or bowel obstruction. In those with EGID, the stomach and the small intestine are the most frequently involved areas. Many patients have history of atopy and food allergy at the time of diagnosis. Endoscopy findings are often variable and not diagnostic. The ultimate diagnosis depends upon histopathologic examination of the involved tissue.

There is no standard therapy for EGE and EC. Steroids are frequently used as the first line of treatment along with dietary restriction. The long-term use of steroids in children is always of concern due to the effects on growth and development. In addition, many patients relapse with steroid withdrawal. Recently, there is more emphasis on steroid-sparing treatment. Mast cell stabilizers and leukotriene inhibitors have shown promise in some studies, while biologic therapies, including humanized anti-IL-5 antibodies reslizumab and mepolizumab, have demonstrated some efficacy in clinical trials. Newer biologic medications targeting specific points along the inflammatory cascade are on the horizon. Despite many strides forward and heightened awareness of EGID, much of the natural history still remains unknown. Further studies to understand the pathophysiology and underlying immune mechanisms will be helpful in delineating the optimal management of these disorders in the future.

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