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GASTROINTESTINAL EOSINOPHILIA

Li Zuo, M.D. and Marc E. Rothenberg, M.D., Ph.D.

Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, College of Medicine, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039.

SYNOPSIS

Gastrointestinal eosinophilia, as a broad term for abnormal eosinophil accumulation in the GI tract, involves many different disease identities. These diseases include primary eosinophil associated gastrointestinal diseases, gastrointestinal eosinophilia in HES and all gastrointestinal eosinophilic states associated with known causes. Each of these diseases has its unique features but there is no absolute boundary between them. All three groups of GI eosinophila are described in this chapter although the focus is on primary gastrointestinal eosinophilia, i.e. EGID.

Keywords

Eosinophil; gastrointestinal; inflammation; pathogenesis; therapy

INTRODUCTION

The presence of eosinophils in tissues and blood is a physiological phenomenon. Eosinophils have roles in both host defense and pathological processes even though we are still not certain about their overall function. A unique feature of eosinophils is that they largely reside in the tissues, instead of staying in the blood circulation like neutrophils do. In fact, the gastrointestinal (GI) tract is a primary site for normal eosinophil residence. Significant progress has been made in elucidating that eosinophils are integral members of the GI mucosal immune system. In physiological states, small numbers of eosinophils are found throughout the GI tract except esophagus. Gastrointestinal eosinophilia is a broad term for any abnormal eosinophil accumulation in the GI system induced in diverse states. In this chapter, we will group GI eosinophilia into three categories: First, primary GI eosinophilia, also termed eosinophil associated gastrointestinal disorders (EGID). These diseases selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia. These disorders include eosinophilic esophagitis (EE), eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis, and are being increasingly recognized; second, GI eosinophilia resulting from hypereosinophilic syndrome (HES); and third, GI eosinophilia triggered by other known causes of eosinophilia, such as drug reactions, parasitic infections, malignancy, etc. All three groups of GI eosinophila will

Corresponding Author: Marc E. Rothenberg M.D., Ph.D, Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, College of Medicine, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039. 513 636-7210 (phone), 513 636 3310 (Fax), and Rothenberg@cchmc.org.

Coauthor: Li Zuo M.D., Division of Allergy and Immunology, Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039. 513 636-2745 (phone), 513 636 4615 (Fax), and Li.Zuo@cchmc.org.

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be described in this chapter although the focus will be on primary gastrointestinal eosinophilia, i.e. EGID. (Figure 1)

PHYSIOLOGICAL PRESENCE OF EOSINOPHILS IN THE GASTROINTESTINAL TRACT

Even though eosinophils have been noted to be present at low levels in numerous tissues as well as in the blood circulation, when a large series of biopsy and autopsy specimens were analyzed, the only organs that demonstrated tissue eosinophils (at substantial levels) were the GI tract, spleen, lymph nodes, and thymus.[1] Notably, eosinophil infiltrations were only associated with eosinophil degranulation in the GI tract. Examination of eosinophils throughout the GI tract of conventional healthy mice (untreated mice maintained under pathogen-free conditions) has revealed that eosinophils are normally present in the lamina propria of the stomach, small intestine, cecum, and colon.[2] Notably, unlike intestinal lymphocytes and mast cells, eosinophils are not normally present in Peyer's patches or intra-epithelial locations, although they commonly infiltrate these regions in primary GI eosinophilia.[3] Data have suggested that eosinophils respond to distinct stimuli compared with other intestinal leukocytes;[2] constitutive expression of eotaxin-1 has also been demonstrated to provide the unique signal that promotes localization of eosinophils into the GI tract at baseline. A recent study has shown that tissue-dwelling eosinophils have distinct cytokine expression patterns under inflammatory or non-inflammatory conditions, with esophageal eosinophils from eosinophilic esophagitis patients expressing relatively high levels of Th2 cytokines.[4]

FUNCTION OF EOSINOPHILIA IN THE GASTROINTESTINAL SYSTEM

Despite the significant progress in histological studies of GI eosinophilia, the function of eosinophils in GI tract is still not well understood. In general, eosinophils play both protective and pathological roles in the GI tract. As part of their protective role, eosinophils are involved in host response against parasitic infections. As part of their involvement in eliciting tissue pathology, allergen-triggered Th2 responses, mediated by IL-5 and IL-13 (for example) have been shown to elicit esophageal pathology, at least in the setting of experimental models in mice. These pathological changes can induce fixed structural lesions such as stricture. In vitro studies have shown that eosinophil granule constituents are toxic to a variety of tissues including intestinal epithelium.[5] Eosinophil granules contain a crystalloid core composed of major basic protein (MBP)-1 (and MBP-2), and a matrix composed of eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO).[6] These cationic proteins share certain pro-inflammatory properties but differ in other ways. For example, MBP, EPO, and ECP have cytotoxic effects on epithelium, in concentrations similar to those found in biological fluids from patients with eosinophilia. Additionally, ECP and EDN belong to the Ribonuclease A superfamily and possess anti-viral and ribonuclease activity. [7,8] ECP can insert voltage insensitive, ion-nonselective toxic pores into the membranes of target cells and these pores may facilitate the entry of other toxic molecules.[9] MBP directly increases smooth muscle reactivity by causing dysfunction of vagal muscarinic M2 receptors. [10] MBP also triggers degranulation of mast cells and basophils. Triggering of eosinophils by engagement of receptors for cytokines, immunoglobulins, and complement can lead to the generation of a wide range of inflammatory cytokines including IL-1, -3, -4, -5, -13, GM-CSF, transforming growth factors, TNF- α , RANTES, MIP-1 α , vascular endothelial cell growth factor, and eotaxin-1, indicating that they have the potential to modulate multiple aspects of the immune response.[11] In fact, eosinophil-derived transforming growth factor- β is linked with epithelial growth, fibrosis, and tissue remodeling.[12,13] Eosinophils express MHC class-II molecules, relevant co-stimulatory molecules (CD40, CD28, B7.1 and B7.2) and secrete an array of cytokines capable of promoting lymphocyte proliferation, activation and Th1 or Th2 polarization (IL-2, IL-4, IL-6, IL-12, IL-10). [11,14-17] Further eosinophil-mediated damage

is caused by toxic hydrogen peroxide and halide acids generated by EPO and by superoxide generated by the respiratory burst oxidase enzyme pathway in eosinophils. Eosinophils also generate large amounts of the LTC₄, which is metabolized to LTD₄ and LTE₄. These three lipid mediators increase vascular permeability and mucus secretion, and are potent stimulators of smooth muscle contraction.[18] Clinical investigations have demonstrated extracellular deposition of MBP and ECP in the small bowel of patients with eosinophilic gastroenteritis and have shown a correlation between the level of eosinophils and disease severity. Electron microscopy studies have revealed ultrastructural changes in the secondary granules (indicative of eosinophil degranulation and mediator release) in duodenal samples from patients with eosinophilic gastroenteritis.[19] Furthermore, Charcot-Leyden crystals, remnants of eosinophil degranulation, are commonly found on microscopic examination of stools obtained from patients with eosinophilic gastroenteritis.[20,21]

Evidence has also supported the association between eosinophils and the enteric nervous system, contributing to the pathogenesis of disease. A recent human study showed the close association of mucosal eosinophils and their granule proteins with the myenteric ganglia. In vitro study also showed the effect of eosinophils on the activation of nerves as well as on nerve remodeling, including the increase of adhesion molecules, muscarinic M2 receptors and nerve growth factor production. Therefore it is possible that the eosinophil-enteric nerve interaction contribute to the intestinal dysmotility that occurs in EGID.

PRIMARY GASTROINTESTINAL EOSINOPHILIA

Patients with EGID suffer from a variety of problems including failure to thrive, abdominal pain, irritability, gastric dysmotility, vomiting, diarrhea, and dysphagia. [22,23] Even though the term “primary” is used here, evidence is accumulating supporting the concept that EGID arises secondary to the interplay of genetic and environmental factors. Notably, a large percentage (~10%) of patients suffering from EGID have an immediate family member with EGID.[22] Additionally, several lines of evidence support an allergic etiology including the finding that ~75% of patients with EGID are atopic, [21,24-30] that the severity of disease can sometimes be reversed by institution of an allergen-free diet,[29-31] and the common finding of mast cell degranulation in tissue specimens.[32,33] Importantly, our recent models of EGID support a potential allergic etiology for these disorders.[34] Interestingly, despite the common finding of food-specific IgE in patients with EGID, food-induced anaphylactic responses occur in only a minority of patients.[19,35] Thus, EGID have properties that fall between pure IgE-mediated food allergy and cellular-mediated hypersensitivity disorders (e.g. Celiac disease). [35]

Although the incidence of primary EGID has not been rigorously calculated, a mini-epidemic of these diseases (especially EE) has been noted over the last decade. [36][37] For example, EE is a global health disease now reported in Australia,[38] Brazil,[39] England,[40] Italy, [41] Japan,[42] Spain[43][44] and Switzerland.[45] Liacouras and his group at Children's Hospital of Philadelphia have found that ~10% of their pediatric patients with GERD-like symptoms who are unresponsive to acid blockade have EE.[46][47] Furuta and his colleagues at Boston Children's Hospital have reported that 6% of their patients with esophagitis have EE. [48] Over a 16-year observation period, Straumann and his colleagues have documented a prevalence of ~1:4000 adults in Switzerland.[4] Croese and colleagues have reported EE to be present in 1:70,000 adults in an Australian provincial city.[39] Finally, we have noted that EE occurs in 1:2,000 children in the Cincinnati metropolitan area over a 5 year time period [49] (and unpublished findings). Collectively, these epidemiological results indicate that EGID is not an uncommon group of diseases, and may have a combined prevalence even higher than pediatric IBD.

Evaluation for EGID

Patients with EGID present with a variety of clinical problems, most commonly failure to thrive, abdominal pain, irritability, gastric dysmotility, vomiting, diarrhea, dysphagia, microcytic anemia, and hypoproteinemia. [22] A diagnostic evaluation for EGID should be performed on all patients with these refractory problems, especially in individuals with a strong history of allergic diseases, peripheral blood eosinophilia, and/or a family history of EGID. Depending upon the intestinal segment involved, the frequency of specific symptoms varies (e.g. abdominal pain and dysphagia are most common in eosinophilic gastroenteritis and EE, respectively), but there are no pathognomonic symptoms or blood tests for diagnosing EGID. Notably, blood eosinophil counts are normal in the majority of patients. If EGID is suspected (based on clinical presentation or evaluation of endoscopic biopsies), then additional testing should be considered to rule out the possibility that there may be another primary disease process such as drug hypersensitivity, collagen-vascular disease, malignancy, or infection.

The evaluation for EGID starts with a comprehensive history and physical examination. Evaluation for intestinal parasites by examination of stool samples, intestinal aspirates obtained during colonoscopy, or specific blood antibody titres should be performed, especially when patients have high-risk exposure (e.g. living on farms or drinking well water). For example, in one series of patients with eosinophilic enteritis, the common dog hookworm *Ancylostoma caninum* (identified by endoscopic detection) has been shown to be the cause of eosinophilic enteritis in 15% of patients,[50] raising the possibility that other occult infections may be involved in the pathogenesis of other apparent cases of EGID. As a precaution, before using systemic immunosuppression for EGID, infection with *Strongyloides stercoralis* should be ruled out, since this infection can become life-threatening in the setting of systemic immunosuppression.[51] The evaluation of total IgE levels has significance in stratifying patients with atopic variants of EGID or suggesting further consideration for occult parasitic infections. Notably, skin prick testing to a panel of food and aeroallergens helps to identify sensitizations to specific allergens. Indeed, patients with the atopic variant of EGID have evidence of IgE sensitization to a mean of 14 different food groups.[22] A preliminary study has suggested a value for delayed cutaneous hypersensitivity testing (skin patch testing) for specific food antigens, in further identifying allergic variants of EE.[30]

The diagnosis of EGID is dependent upon the microscopic evaluation of endoscopic biopsy samples, with careful attention to the quantity, location, and characteristics of the eosinophilic inflammation. Patients with EGID often present with a clear history and positive biopsy results for the disease but have a variety of endoscopic findings.[52] It is not uncommon for endoscopic appearances of the gastrointestinal tract to look normal; thus, microscopic evaluation of biopsy samples is essential. Furthermore, the disease often has patchy involvement, necessitating the analysis of multiple endoscopic biopsies from each intestinal segment.[53] Because no widely accepted diagnostic criteria has been established for EGID, the diagnosis is dependent upon the expertise of the physicians involved in the evaluation of the biopsy samples. While the normal esophagus is devoid of eosinophils, the rest of the gastrointestinal tract contains readily detectable eosinophils.[54] Thus, differentiation of EGID from the normal condition relies on several factors including (1) eosinophil quantification (and comparisons to normal values at each medical center); (2) the location of eosinophils (e.g. their presence in abnormal positions such as the intra-epithelial and intestinal crypt regions); (3) associated pathological abnormalities (e.g. epithelial hyperplasia as in the case of EE), and (4) the absence of pathological features suggestive of other primary disorders (e.g. neutrophilia associated with IBD, or vasculitis associated with Churg-Strauss syndrome). Based on these criteria, patients often suffer from symptoms for an extended period of time (mean of 4 years) before a bona fide diagnosis of EGID is established.[22]

Eosinophilic Esophagitis

Among all primary gastrointestinal eosinophilic diseases, EE is unique due to the fact that the esophagus in a healthy individual is completely devoid of eosinophils, not like other parts of GI tract.[55] Therefore, any eosinophils in the esophagus may indicate a disease process. In general, esophageal eosinophil numbers in EE are much higher than in GERD. The diagnosis of EE is usually defined as a positive esophageal biopsy showing more than 15 eosinophils/HPF. In most cases, esophageal eosinophil numbers in GERD is under 7 and the concurrence of GERD and allergy may have 7-20 eosinophils/HPF. However, a recent study by Ngo et al. reported three GERD patients with esophageal eosinophil numbers between 21-52/HPF who were successfully treated with a proton pump inhibitor.[56] The key difference between EE and GERD is not the absolute numbers of eosinophils in the esophagus. Instead, EE patients will have persistent esophageal eosinophilia even with proton pump inhibitor treatment.

Treatment of EGID

Principles of treatment for EE, eosinophilic gastroenteritis and colitis are similar. Eliminating the dietary intake of the foods implicated by skin prick testing (or RAST testing) has variable effects, but complete resolution is generally achieved with an amino acid-based elemental diet. [57] Once disease remission has been obtained by dietary modification, the specific food groups are slowly reintroduced (at ~3 week intervals for each food group) and endoscopy is performed every 3 months, to identify sustained remission or disease flare-up. Drugs such as cromoglycate, montelukast, ketotifen, suplatast tosilate, mycophenolate mofetil (a inosine monophosphate dehydrogenase inhibitor), and “alternative Chinese medicines” have been advocated,[22,23] but are generally not successful in the author's experience. In our institution, an appropriate therapeutic approach includes a trial of food elimination if sensitization is found by food skin testing and/or RAST. If no sensitization is found or if specific food avoidance is not feasible, an elemental formula is instituted. Up to now, the management of EGIDs, besides elemental diet as mentioned above, includes four parts: systemic and topical steroids, non-corticosteroid therapy, management of other EGID complications (such as iron deficiency and anemia) and the management of therapeutic toxicity.[59] Anti-inflammatory drugs (systemic or topical steroids) are the main therapy in cases where diet restriction is not feasible or has failed to improve the disease. For systemic steroid therapy, a course of 2 to 6 weeks of therapy with relatively low doses seems to work better than a 7-day course of burst glucocorticoids. There are several forms of topical glucocorticoids designed to deliver drugs to specific segments of the gastrointestinal tract (e.g. budesonide tablets [Entocort™ EC] designed to deliver drug to the ileum and proximal colon). As with asthmatic treatment, topical steroids have a better benefit-to-risk effect compared to systemic steroids. Currently, anti-IL-5 and anti-IgE trials are in progress and some studies have shown promising results.[60] In severe cases refractory or dependent upon glucocorticoid therapy, intravenous alimentation or immunosuppressive antimetabolite therapy (azathioprine or 6-mercaptopurine) are alternatives. Finally, even if GERD is not present, neutralization of gastric acidity (with proton pump inhibitors) may improve symptoms and the degree of esophageal and gastric pathology.

GASTROINTESTINAL EOSINOPHILIA IN HYPEREOSINOPHILIC SYNDROME (HES)

The term HES, was introduced by Anderson and Hardy in 1968 to designate patients with marked eosinophilia in the absence of other causes of eosinophilia.[61] They reported three patients, all males, between the ages of 34 to 47 who suffered from cardiopulmonary symptoms, fever, sweats, weight loss and marked eosinophilia. Two of the patients died, and at autopsy, their hearts were enlarged and showed mural thrombi. Multiple organs are involved in HES, including heart, lung, skin, nervous system, and GI system. Due to the involvement of the GI system, HES may be confused with EGID. However, HES usually involves many other organs

with heart, skin, and CNS as its major target organs. The treatment for HES is similar to those utilized for patients with chronic myelogenous leukemia, including prednisone, hydroxyurea, and interferon- α . Chusid and his associates formulated the diagnostic criteria for HES to include (1) persistent eosinophilia of at least 1500 cells/mm² for a minimum of six months; (2) lack of known causes for eosinophilia (e.g. parasitic or allergic triggers); and (3) symptoms and signs of organ system involvement.[62] Based on these diagnostic criteria, patients with EGID and blood eosinophil counts >1500/mm² meet the diagnostic criteria. However, patients with EGID generally do not have the high risk of life-threatening complications associated with classic HES (i.e. the cardiomyopathy, or central nervous system involvement). Notably, considerable heterogeneity among HES patients has been recognized. For example, T cell clones producing the characteristic Th2 cytokines, IL-4 and IL-5, have been found in patients satisfying the diagnostic criteria for HES.[63,64] However, perhaps the most striking advance in our understanding of HES has resulted from treatment of HES patients with the tyrosine kinase inhibitor, imatinib mesylate.[65-69] Imatinib was introduced for the treatment of chronic myelogenous leukemia and has had a remarkable effect in that disease. Treatment of many HES patients with imatinib mesylate causes a dramatic reduction of peripheral blood and bone marrow eosinophils suggesting that certain HES patients express a novel kinase sensitive to imatinib mesylate. Further investigation of the ability of imatinib mesylate to treat HES patients revealed the existence of an 800 kilobase deletion in chromosome 4 bringing together an upstream DNA sequence homologous to a yeast protein, referred to as FIP1, and designated as like FIP1, or FIP1-L1 and the gene for the cytoplasmic domain of the platelet derived growth factor alpha (PDGFRA) receptor.[65,70] This fusion gene is transcribed and translated yielding a novel kinase referred to as FIP-L1-PDGFRA; FIP-L1-PDGFRA is exquisitely sensitive to imatinib in vitro, thus explaining the remarkable sensitivity of HES patients to this drug. The FIP-L1-PDGFRA fusion gene cooperates with IL-5 overexpression in a murine model of HES, suggesting that both pathogenic events cooperate in disease etiology.[71] The patients generally responsive to imatinib are those most characteristic of "classic" HES, namely males between the ages of 20-50 who present clinically with marked peripheral blood eosinophilia. Recently, these patients have been shown to meet minor criteria for systemic mastocytosis, having elevated levels of serum mast cell tryptase, and high numbers of dysplastic mast cells in the bone marrow.[72,73] These patients go on to develop eosinophilic endomyocardial disease with embolization to peripheral organs including the extremities and the brain, and they strikingly resemble the patients originally designated by Hardy and Anderson.[61] However, it appears that any disease that results in prolonged and marked eosinophilia can be associated with endomyocardial disease. For example, endomyocardial disease has occurred during the course of helminth infections and also in various malignancies associated with marked eosinophilia.[74-76] Thus, patients with marked eosinophilia are at risk for the development of cardiac disease regardless of the underlying etiology of the eosinophilia. Accordingly, routine surveillance of the cardio-respiratory system (e.g. echocardiograms and plethysmography) in patients with EGID and peripheral blood eosinophilia is warranted. Based on these concerns, the diagnosis of HES in patients with EGID should always be considered especially in patients who develop extra-gastrointestinal manifestations (e.g. splenomegaly, or cutaneous, cardiac, or respiratory systems). As such, additional diagnostic testing for HES should be considered including bone marrow analysis (searching for evidence of myelodysplasia), serum mast cell tryptase and vitamin B12 levels (both moderately elevated in classic HES), and genetic analysis for the presence of the FIP1L1-PDGFRA fusion event.[72]

GASTROINTESTINAL EOSINOPHILIA FROM KNOWN CAUSES

There are a variety of other known causes of GI eosinophilia, including parasitic infections, other allergic disorders, gastrointestinal reflux disease (GERD), inflammatory bowel diseases, drug reactions, malignancy, Churg-Stauss syndrome, celiac disease, systemic lupus

erythematosus (SLE) and solid organ transplantation. Among those causes, parasitic infections are the most common cause of gastrointestinal eosinophilia in developing countries. In developed countries, allergic causes have become the dominant cause for gastrointestinal eosinophilia. Among the infectious causes of gastrointestinal eosinophilia, aside from the number one cause parasitic infections, helicobacter pylori infection has also been reported. Medications causing GI eosinophilia include gold salts, azathioprine, gemfibrozil, enalapril, carbamazepine, clofazimine and cotrimoxazole. In the Churg-Strauss syndrome and polyarteritis nodosa, characterized findings include eosinophilic infiltrate involving the small vessels in the intestinal tract and other organs. In IBD, eosinophils usually represent only a small percentage of the infiltrating leukocytes,[77,78] but their level has been proposed to be a negative prognostic indicator.[78,79]

CONCLUSION

Gastrointestinal eosinophilia, as a broad term for abnormal eosinophil accumulation in the GI tract, involves many different disease identities. These diseases include primary eosinophil associated gastrointestinal diseases, gastrointestinal eosinophilia in HES and all gastrointestinal eosinophilic states associated with known causes. Although each of these diseases has its unique features, it is important to recognize that there is no absolute boundary between them. As an example, HES is a systemic eosinophilic disease but it may also involve the gastrointestinal tract and not be associated with apparent causes as in primary gastrointestinal eosinophilia. Similarly, primary EGID has a strong association with allergy, yet it is generally not considered a secondary eosinophilia. Indeed, different disease mechanisms likely account for these various states. For example, the eosinophilic esophagitis appears to be primarily driven by IL-5 and eotaxin-3, whereas evidence is emerging that eosinophilic enteritis may be primarily driven by eotaxin-1. As such, targeted therapy with anti-eotaxins, eotaxin receptor blockers (e.g. CCR3 antagonists), or humanized anti-IL-5 therapeutics are likely to be useful therapy in the future. Indeed, early clinical trials have supported their potential utility[60].

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Abbreviations

ECP, Eosinophil cationic protein; EDN, Eosinophil derived neurotoxin; EE, Eosinophilic esophagitis; EGID, Eosinophilic gastrointestinal disorders; EPO, Eosinophil peroxidase; GERD, Gastroesophageal reflux disease; GI, Gastrointestinal; GM-CSF, Granulocyte-macrophage colony stimulating factor; HES, Hypereosinophilic syndrome; IBD, Inflammatory bowel disease; LTC, Cysteinyl leukotriene; MBP, Major Basic Protein.

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Figure 1.
Gastrointestinal Eosinophilia