Eosinophilic Disorders of Childhood

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Introduction

Allergy and eosinophilia in the gastrointestinal (GI) tract are not equivalent. GI eosinophilia is associated with infections (parasites), nutritional deficiencies, inflammatory processes, neoplasias, and systemic disorders. However, in addition to eosinophilia, other histologic changes usually accompany the increased number of eosinophils in most of these conditions. In contrast, there is a group of GI disorders that are primarily or exclusively characterized by tissue eosinophilia in the absence of known causes for eosinophilia. These primary eosinophilic GI disorders include eosinophilic esophagitis (EoE), allergic proctocolitis, and eosinophilic gastroenteritis. Several lines of evidence support an allergic cause for these disorders but in many patients a specific allergen is not easily identified..

Baseline eosinophils are normally found in the GI tract, specifically in the stomach, small bowel, and large intestine. Eosinophils are present prenatally. They convey antiparasite immunity, release cytotoxic granule proteins and, by interacting with T-cells, aid in antigen presentation, proliferation, and maturation and regulate T-cell responses. Normal levels in the GI tract range from ~5 eosinophils/high-powered field (HPF) in the stomach antrum and fundus to ~35 eosinophils/HPF in the cecum. Geographic variations have been found in the level of eosinophils in the GI mucosa. In addition to their number (subject to the known geographic variation), factors that determine whether eosinophils found in the GI tract should be considered "abnormal" include, their location (superficial vs deep; intraepithelial vs lamina propria), the finding of free granules, and the presence of associated pathologic abnormalities, such as epithelial changes, neutrophilia, and lymphocytosis.

Food allergy is believed to affect 2% to 8% of children younger than 2 years of age. It has been estimated to be the most frequent cause of chronic diarrhea in infancy in the U.S. The foreign antigenic substances are mainly cow's milk in the infant and egg and soy protein in the older child. There is evidence that minute amounts of substances in breast milk may act as allergens in the infant. Many of these allergic reactions are temporary and appear to wane with age. Cross-reactivity between substances causing gastrointestinal and respiratory allergic reactions has been demonstrated. Predisposing factors in the child include a family history of atopy, IgA deficiency, early exposure to the antigen, and preceding gastrointestinal infection, possibly even including infection by *Helicobacter pylori*.

Food allergy can be mediated by type I, type III, or type IV immune reactions, singly or in combination. Type I reactions are of immediate onset and are associated with

mast cell degranulation and elevated IgE antibodies. Though infrequently documented on biopsy samples mucosal reactions are characterized by edema and altered motility and permeability. Type III (immune-complex) reactions are not believed to play a major role in food allergy, though they have been reported on occasion. Type IV, or cell-mediated reactions, result in the production of increased levels of IL-4, IL-5, and interferon-gamma, eosinophil chemoattractants secreted by activated lymphocytes and by eosinophils in an autocrine fashion all of which modulate eosinophil recruitment to the gut, the salient histologic feature of allergic enteropathy. In general, allergic disorders affecting the gut are non-IgE-mediated.

A clinical classification of food hypersensitivity reactions has been recently proposed and is presented in Table 1.

TABLE 1. Classification of Gastrointestinal Food Hypersensitivity.

IgE-mediated disorders
- Immediate gastrointestinal hypersensitivity
- Oral allergy syndrome

Mixed IgE and non-IgE-mediated disorders
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis

Non-IgE-mediated disorders
- Dietary protein (allergic) colitis and proctitis
- Dietary protein enteropathy
- Celiac disease

Source: Adapted from Sampson HA and Anderson JA.

Eosinophilic Disorders of the GI Tract

Eosinophilic Esophagitis

Over the last decade, it has been recognized that not all cases that present with symptoms of GER and have associated esophageal eosinophilia represent gastroesophageal reflux disease. A number of studies have described a unique group of patients with eosinophilic esophagitis who present with symptoms that are otherwise indistinguishable from those secondary to reflux esophagitis but fail to respond to conventional antireflux therapy. The degree of eosinophilia in this patient population tends to be unusually severe, greater than 20 eosinophils per high-magnification microscopic field. The symptoms as well as the histologic abnormalities frequently improve with either steroid or restricted diet therapy. On the basis of these observations and the frequent extra-intestinal allergic symptoms (asthma, eczema, and chronic rhinitis) experienced by these patients, an allergic etiology for this type of esophagitis has been proposed. However, one of the difficulties in establishing the actual etiology of this form of eosinophilic esophagitis is that in many patients a specific allergen is not easily identified. This form of esophagitis is usually referred as EoE.

While esophageal histology is essential in making the diagnosis of EoE, in some cases, endoscopy may reveal either a ringed appearance or linear furrows; however, these visual features are not pathognomonic for EoE. In some patients, superficial eosinophilic microabscesses in the squamous epithelium give the esophagus an endoscopic appearance characterized by white punctate lesions or a white exudates, which may be initially misinterpreted as Candida esophagitis. The main features of EoE are listed in Table 2.

In patients with EoE, the histologic changes are similar to reflux esophagitis, but the number of intraepithelial eosinophils is usually higher, frequently more than 20 eosinophils per high-magnification microscopic fields. Liacouras et al demonstrated that the clinical and histologic features of allergic esophagitis might evolve over years. Some patients may actually remain asymptomatic and present late in the course of the disease with dysphagia secondary to strictures. When eosinophilic infiltration is not confined to the esophagus but involves other segments of the gastrointestinal tract, classic eosinophilic gastroenteritis should be considered. Whether EoE is a variant of eosinophilic gastroenteritis or represents a different process is not clear.

TABLE 2. Eosinophilic Esophagitis.

Gastrointestinal symptoms	Vomiting and regurgitation
	Epigastric and chest pain
	Heartburn
	Nausea
	Dysphagia
Extra-intestinal symptoms	Asthma
	Eczema
	Chronic rhinitis
24-hour, pH probe testing	Normal
Histology	Severe esophageal eosinophilia
Treatment	Unresponsive to anti-reflux therapy
	Responsive to steroids and restricted diet

Because EoE has only recently been recognized, both acute and long-term complications have been difficult to assess. However, a review of the literature suggests that while EoE has been mainly documented in children, it also occurs in adults. Adults identified with this disorder often suffer from significant dysphagia and the development of esophageal strictures. Thus, if EoE is left untreated in childhood, it may cause future signs and symptoms as have been seen in adults.

While initial reports have demonstrated that the disease responds to corticosteroid therapy, either taken orally or by swallowed inhalation therapy, many studies have demonstrated a high rate of recurrence after discontinuation of therapy. Recently, patients have been found to respond to a food elimination diet using an elementary formula, which results in complete resolution of esophageal eosinophilia and its corresponding symptoms.

Allergic Proctocolitis

Infants with allergic proctocolitis typically present during the first 2 months of life with blood-streaked stools, which may lead to a consideration of an anal fissure or tear. Growth is usually not affected, and peripheral eosinophilia is variable. Breast-fed infants may present at an older age and have less severe symptoms. The diagnosis in an infant fed cow's milk or commercial formulas is relatively straightforward. Biopsies are performed to rule out other causes of bloody diarrhea in the infant such as infections and Hirschsprung–associated colitis.

Endoscopic features include erythema, mucosal friability, focal erosions, and nodularity, the latter suggestive of nodular lymphoid hyperplasia. Disease is usually limited to the distal colon. Eosinophils may be observed in stool smears, which should also be obtained to detect parasitic infection. Increased numbers of eosinophils, frequently clustered and some times accompanied by neutrophils, are characteristically noted in all compartments of the mucosa in biopsies. The number of eosinophils is variable, reportedly ranging from greater than 6 to more than 20 per high power field, and is frequently a focal finding. Eosinophil numbers may also vary as a result of dietary withdrawal therapies often empirically attempted prior to obtaining the biopsies. Infiltration of crypt and surface epithelium is generally readily noted and is an important diagnostic feature. The mucosal architecture is well preserved. Significant crypt architectural distorsion is distinctly unusual and, if present, should suggest other disorders. Nodular lymphoid hyperplasia is a frequent concomitant finding. The differential diagnosis includes parasitic infections such as *Dientamoeba fragilis*, which can be identified in stool smears. It should be pointed out that eosinophilic infiltrates can also be seen in cases of Hirschsprung disease and that, conversely, the clinical and radiologic features of allergic colitis can occasionally mimic aganglionosis. The treatment is dietary change to a hypoallergenic formula. The condition is temporary; most patients can tolerate milk after 2 years of age.

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis involves eosinophilic infiltration throughout the GI tract. It is a rare condition, the etiology of which is unknown, and is the most difficult to treat eosinophilic disorder of the GI tract. Eosinophilic gastroenteritis is, in the broadest sense, a histological observation based upon a mostly subjective impression of increased eosinophils, usually seen in a biopsy sample of the intestine or colon where eosinophils normally reside. Pediatric patients of all ages have been reported, as well as adults, presenting with a bewildering array of clinical manifestations. Peripheral eosinophilia may be, but not always, elevated. Corroborating tests such as the detection of allergen-specific IgE antibodies, by pinprick or by in-vitro radioallergosorbent testing (RAST), are of varying diagnostic usefulness. Numerous case reports document unusual manifestations such as pancreatitis, pyloric stenosis, abdominal mass, intestinal perforation, and duodenal ulcers.

This situation is complicated by the absence of well-defined criteria for an objective assessment of increased eosinophils, especially in the intestinal and colonic mucosa, by the fact that increased numbers of eosinophils can be observed in diseases other than allergic, and by the difficulty in substantiating in an unequivocal manner an allergic etiology in many cases. The difficulty in establishing the diagnosis by histologic examination results from the variability in normal eosinophil counts, as well as by the variability in eosinophilic infiltration even in established disease. Mucosal eosinophil counts in the normal intestine and colon vary according to site, age, geographic location, and even time of year. Establishing the diagnosis histologically is thus fraught with difficulty and should not be attempted without clinical and laboratory correlation.

A greater degree of confidence in the diagnosis is justified in the presence of marked eosinophilic infiltration or large clusters of eosinophils, with epithelial infiltration and damage. Furthermore, increased eosinophils in the gastric body and antrum, where eosinophil counts are usually low, may be a more reliable marker. Perhaps the greatest value of the biopsy is to identify causes other than allergy for the patient's symptoms.

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