

Histopathologic Diagnosis of Eosinophilic Conditions in the Gastrointestinal Tract

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Abstract: Eosinophils, a constitutive component of the columnar-lined gastrointestinal tract, play an essential role in allergic responses and parasitic infections. The tissue density of these cells also increases in a variety of conditions of uncertain etiology. With the exception of the esophageal squamous epithelium, in which no eosinophils are normally present, the population of normal eosinophils in the remainder of the luminal gut is poorly defined. Therefore, histopathologists must rely on their subjective judgment to determine when a diagnosis of eosinophilic gastritis, enteritis, or colitis should be rendered. Eosinophilic esophagitis is currently the best defined and most studied eosinophilic condition of the digestive tract; therefore, the confidence in accurate diagnosis is increasing. In contrast, the characteristic clinicopathologic features of eosinophilic conditions affecting other parts of the digestive tract remain somewhat elusive. This review was designed to present pathologists with simple and practical information for the biopsy-based histopathologic diagnosis of eosinophilic esophagitis, gastritis, enteritis, and colitis. It was prepared by critically reviewing more than 200 articles on the topic, along with incorporating evidence accumulated through our own collective experience. We anticipate that by increasing pathologists' confidence in reporting these abnormal but often nameless eosinophilic infiltrates, we can help better define and characterize their significance.

Key Words: eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, eosinophilic colitis, intestinal parasites, gastrointestinal pathology, eosinophils

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The recent categorization of eosinophilic esophagitis as a distinct condition with well-defined clinical and histopathologic criteria and its undisputable surge during the last decade have heightened our awareness of increased eosinophilic infiltrates in other segments of the gastrointestinal (GI) tract. In contrast to the squamous mucosa of the esophagus, the lamina propria of all other segments of the GI tract contains constitutive eosinophils. The number of intramucosal eosinophils is believed to vary widely among normal individuals, depending on age, exposure to food allergens, geography, and exposure to infectious agents. Furthermore, eosinophil counts in the same individual vary within different portions of an organ, for example, the cecum versus the sigmoid colon. Thus far, what constitutes the normal eosinophilic infiltrates in the stomach, small intestine, and colon have not been agreed

upon. Consequently, the diagnosis of eosinophilic gastritis, enteritis, or colitis depends more on a pathologist's subjective judgment than on objective criteria.

The purpose of this review is to provide simple and practical data for the biopsy-based histopathologic diagnosis of eosinophilic esophagitis, gastritis, enteritis, and colitis. With the exception of eosinophilic esophagitis, evidence-based guidelines are lacking. Therefore, we have relied on a critical evaluation of the published series and on our personal experience in this area.

THE EOSINOPHIL

The Goddess of the Rosy Fingers

In 1871, Heinrich Caro, a German textile chemist from Mannheim used bromine to bring out a reddish color from fluorescein. In 1874, he named this tetrabromofluorescein compound eosin, in a classic reference to the Greek goddess of dawn Eos, who with her “rosy fingers” opened the gates of heaven every morning so that Apollo could ride his chariot across the sky.¹ Later modified to become soluble in water, the compound became known as “wasserlösliches Eosin” and was one of many dyes used by Ehrlich² to stain blood cells. In 1879 while still a student, Ehrlich described circulating leukocytes with a bilobular nucleus and cytoplasm rich in fine granules that stained pink with eosin, and named them eosinophils. In 1889, Gollasch³ noted an association with asthma, and in 1897, Brown⁴ reported high levels of peripheral and tissue eosinophils in 3 patients infected with *Trichinella spiralis*, followed by a complete account of the observation.⁵ In 1912, Schlecht and Schwenker⁶ consolidated their focus on allergic and anaphylactic conditions. Studies on eosinophils as defense mechanisms against helminthic parasites peaked in the 1970s and 1980s, in parallel with a renewed interest in tropical diseases, and led to fundamental discoveries of the structure and functions of these cells.

The Eosinophil: Structure and Function

Eosinophils are multifunctional proinflammatory cells found in the hematopoietic system and also in certain tissues, including the mucosal and submucosal areas of the GI, respiratory, and genitourinary tracts. The normal range for eosinophils in peripheral blood is 0 to 450 eosinophils/ μ L. Eosinophils are formed in the bone marrow, where they mature in approximately 8 days before moving into the blood. After circulating for 8 to 12 hours, eosinophils reach their destination tissues, with an overall lifespan of 1 to 2 weeks. In rare instances, such as in *erythema toxicum neonatorum*, eosinophils have been shown to play a beneficial modulatory function.^{7,8} However, in many other conditions (eg, Loeffler disease, Churg-Strauss syndrome, and the idiopathic hypereosinophilic syndrome) eosinophils have a critical role in the pathogenesis of tissue damage.^{9,10}

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Eosinophil granule proteins, such as major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin, are capable of inducing tissue damage and dysfunction. MBP, EPO, and ECP have been shown to be toxic to heart, brain, bronchial, and intestinal epithelium.⁷ The degree of tissue injury is related to the duration of eosinophilia, the level of eosinophil activation, and the type of stimulus attracting the eosinophil.^{11–13} An important effect of prolonged eosinophilic inflammation is tissue remodeling. Through secretion of ECP, EPO, and ECP, and a number of cytokines such as transforming growth factor- β 1, phospho-SMAD2/3, and vascular cell adhesion molecule 1, and through interactions with mast cells and epithelial cells, eosinophils have a profibrogenic function. This effect is particularly evident in asthma and eosinophilic esophagitis.^{14–16}

EOSINOPHILS IN THE GASTROINTESTINAL TRACT

The GI tract is a principal target for migration of eosinophils, which are part of the normal component of the lamina propria in the stomach, small intestine, and colon.¹⁷ A number of cytokines and chemokines regulate the traffic of eosinophils in the GI tract, including interleukin-3 (IL-3) and the granulocyte-macrophage colony-stimulating factor.^{18,19} However, the major regulatory role is played by IL-5. IL-5 not only promotes the development, proliferation, and migration of eosinophils in the bone marrow, but also regulates their survival, stimulates degranulation, and primes them for responding to the chemoattractant signals that recruit them to the mucosa. Recent reviews by Strauman²⁰ and Powell et al¹⁷ provide more thorough discussion of the complex interactions of eosinophils with other inflammatory cells in the GI mucosa.

A TECHNICAL NOTE

In an astute systematic review of eosinophilic esophagitis, Dellon et al²¹ noted that in the vast majority of articles published until 2004, results were regularly reported in eosinophils per high-power field (HPF). However, despite the well known variability of the area of a “high-power field” (from <0.100 to >0.400 mm², depending on the eyepiece used), the actual area of measurement is virtually never reported. Thus, comparisons between different studies can be misleading. In this review, our own data are reported in eosinophils/mm². We use a 22 mm eyepiece with a 40×0.75 lens, and our HPF measures 0.237 mm² [$=\pi(22/40/2)^2$]. Thus, the number of eosinophils/mm² is calculated using the formula $n^{\text{HPF}}/0.237$ (where n^{HPF} is the count per HPF). As most published counts are given in numbers of cells per (undefined) HPF, we have reported literature data as stated in the original publications.

ESOPHAGUS

Normal Eosinophil Counts in the Esophageal Mucosa

The squamous mucosa of the normal esophagus does not contain any eosinophils.²⁰ Some purists claim that even a single intraepithelial eosinophil is an indication of reflux-induced damage. A less rigid approach, which we support, suggests that rare eosinophils in close proximity to the squamocolumnar interface are commonly found and should not be attributed any diagnostic significance.

Causes of Esophageal Eosinophilia

The most common clinical situations in which eosinophils infiltrate the esophageal mucosa are gastroesophageal reflux and eosinophilic esophagitis; both are discussed in detail below. Other conditions that have been associated with esophageal eosinophilia include achalasia,²² connective tissue diseases (particularly scleroderma), vasculitis, drug reactions, inflammatory bowel disease (IBD), and malignancies.²³ The esophagus may also be involved by systemic or diffuse GI eosinophilic syndromes [peripheral hypereosinophilic syndrome and eosinophilic gastroenteritis (EGE)]. Although eosinophils may be part of the inflammatory response to fungal infections, they are virtually never the predominant cell type. Although traditionally included among the causes of esophageal eosinophilia, no helminthic infections affect the human esophagus, thus parasites need not be considered. Rare cases of esophageal leiomyomatosis associated with dense eosinophilic infiltration are very likely overlapping with, or possibly an expression of, long-standing eosinophilic esophagitis.^{24,25}

Gastrointestinal Reflux Disorder

Eosinophils may be found in the distal esophagus of patients with documented gastroesophageal reflux disease, albeit in no more than 20% of the cases. These infiltrates are rarely dense, usually consisting of <10 eosinophils/HPF.^{26,27} Eosinophils, typically found only in the distal esophagus, tend to be localized in the basal layer of the squamous epithelium, and do not form microabscesses. However, the distinction from eosinophilic esophagitis is sometimes impossible on histopathologic grounds alone.^{28,29}

Eosinophilic Esophagitis

As recently as five years ago, few pathologists practicing outside specialized centers for esophageal disease were asked to “rule out eosinophilic esophagitis” on a set of biopsies from the esophagus. At that time, only rare case series had been published, almost exclusively in the pediatric literature.³⁰ Pathologists rarely questioned the axiom that eosinophils in the squamous esophageal mucosa equated with reflux. Those who looked for diagnostic criteria for eosinophilic esophagitis were likely rewarded with confusion and further skepticism. However, because of its relatively high and apparently increasing incidence, eosinophilic esophagitis has become the most intensely studied eosinophil-related GI disorder. At the time of this writing a MEDLINE search for “eosinophilic esophagitis” yielded more than 630 articles, 117 of which were published within the last 12 months.

In 2006, a multidisciplinary group with the aims of understanding the pathogenesis of eosinophilic diseases and developing evidence-based diagnostic and therapeutic guidelines for eosinophilic esophagitis gathered at the First International Gastrointestinal Eosinophil Research Symposium (FIGERS).³¹ The FIGERS group proposed criteria based on the number of intraepithelial eosinophils counted by a diligent pathologist in the proverbial (but, alas, rarely measured) HPF. This number had been arbitrarily set at 25 or 20 eosinophils/HPF,^{32,33} but most of the studies referred to eosinophilic esophagitis without detailing the histopathologic criteria are used.²¹ On the basis of extensive literature review and the members’ clinical experience, the FIGERS concluded that at least 1 HPF must contain at least 15 eosinophils. The FIGERS consensus recommendations define eosinophilic esophagitis as a “primary

TABLE 1. Histologic Findings Suggestive of Eosinophilic Esophagitis

Absolute eosinophil count per HPF in at least 1 HPF	≥ 15 eosinophils/HPF
Degranulated eosinophils	Very common
Eosinophilic microabscesses	Defined as clusters of > 4 eosinophils. Frequently present
Distribution of eosinophils within the mucosa	Spread throughout the depth of the biopsies, particularly superficial/luminal
Distribution of eosinophils throughout multiple biopsy sites	Can be patchy, but more often diffuse and involves entire length (lower, mid, and upper) of esophagus
Fibrosis of the underlying lamina propria	Can be seen, especially in long-standing disease

Basal zone hyperplasia, intercellular edema, and elongation of the lamina propria papillae occur in both eosinophilic esophagitis and gastroesophageal reflux disease. HPF indicates high-power field. Adapted from *Gastroenterology*. 2007;133:1342–1363.

clinicopathologic disorder of the esophagus, characterized by esophageal and/or upper GI tract symptoms in association with esophageal mucosal biopsy specimens containing ≥ 15 intraepithelial eosinophils/HPF in 1 or more biopsy specimens and absence of pathologic gastroesophageal reflux disease as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to high-dose proton pump inhibitor medication.³¹ Additional histologic features of eosinophilic esophagitis that should be assessed are listed in Table 1.

Some patients whose esophageal biopsies meet the criteria for eosinophilic esophagitis benefit from therapy with proton-pump inhibitors, whereas others do not.³⁴ Recently, it has even been proposed that proton-pump inhibitors, by causing a loosening of the tight junctions and allowing the absorption of larger allergenic proteins, may contribute to the pathogenesis of eosinophilic esophagitis.³⁵ Furthermore, in addition to acid inhibition, proton pump inhibitors may have anti-inflammatory and antieotaxin-3 activity,³⁶ which could account for their effectiveness in some patients with eosinophilic esophagitis. In light of these and other confounding findings, the required “lack of response to high-dose proton pump inhibitors medication” should probably be deemphasized.

Practical Suggestions for Diagnosis

Clearly, although clinical and endoscopic criteria are important, the diagnosis rests ultimately on finding a set of histopathologic features that an experienced pathologist recognizes as highly suggestive for eosinophilic esophagitis. These findings, summarized in Table 1, include number and distribution of eosinophils within the squamous epithelium, the topographic extension of the eosinophilic infiltrates along the esophagus, and the architectural and maturational changes occurring in the squamous epithelium. As depicted in Figure 1 (A–C), the delineation between eosinophilic and reflux esophagitis is not always straightforward, since both conditions may coexist in the same patient.^{37,38}

When specimens from both distal and middle or proximal esophagus are available and eosinophil counts > 15/HPF are found in both locations, a diagnosis of “compatible with eosinophilic esophagitis” can be made. A

more elaborate comment may be added to the effect that “the histopathologic criteria for the diagnosis of eosinophilic esophagitis are met.” Clinicians can then decide whether the clinical context is appropriate for this diagnosis. Although the FIGERS consensus specifically recommends that biopsies from both the distal and middle or proximal esophagus be obtained if eosinophilic esophagitis

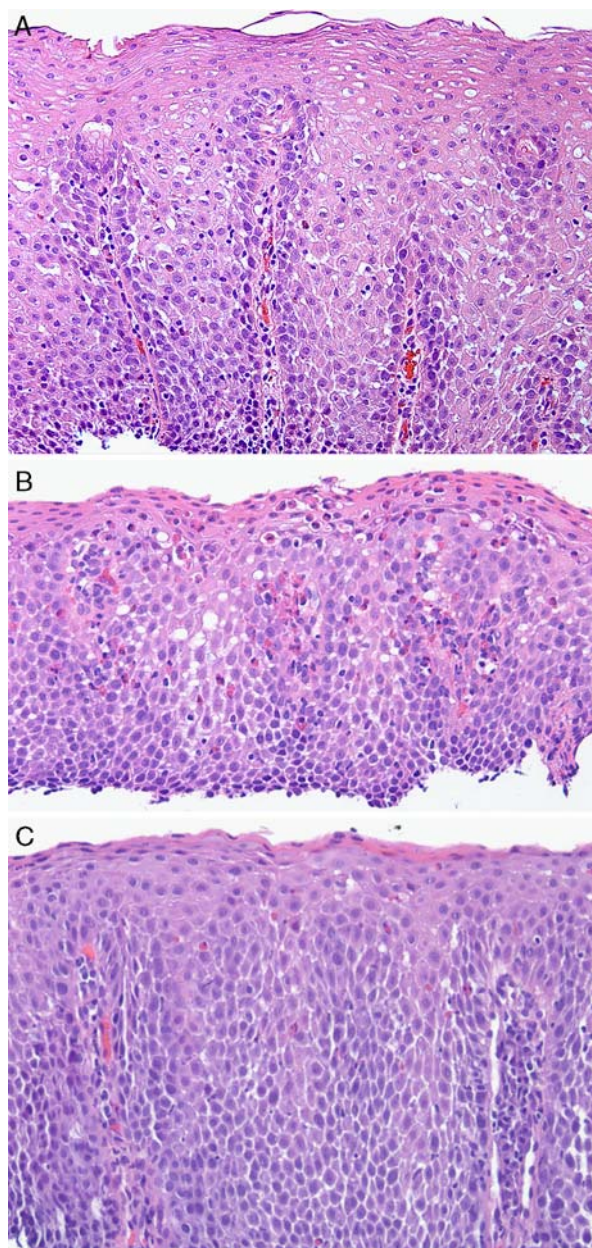


FIGURE 1. Overlapping histopathologic features in gastroesophageal reflux disease and eosinophilic esophagitis include basal cell hyperplasia, intercellular edema, and papillary elongation. A, Reflux esophagitis with few eosinophils, predominantly in the basal portion of the squamous epithelium, and sparse lymphocytes and neutrophils. B, Eosinophilic esophagitis with eosinophilic clustering and eosinophils spread throughout the depth of the squamous mucosa. C, Distal esophagus biopsy with features suggestive of eosinophilic esophagitis but fewer than 15 eosinophils per high-power field.

TABLE 2. Eosinophil Counts in Gastric Biopsies From Three Control Cohorts

	Normal Stomach n = 135	<i>Helicobacter pylori</i> Gastritis n = 93	Crohn Disease n = 53
Median density (eosinophils/HPF)	2	1	1
(Eosinophils/mm ²)	8	5	3
Mean density (eosinophils/HPF)	1	2	2
(Eosinophils/mm ²)	4.9	7.9	9.9
Range (eosinophils/HPF)	0-8	0-16	0-15
(Eosinophils/mm ²)	0-34.6	0-69	0-64

Eosinophil counts in gastric biopsies from patients with unremarkable biopsies, *H. pylori*, or Crohn disease. The cohorts were matched for age, sex, and zip code to a set of patients with markedly increased gastric eosinophils.

HPF indicates high-power field. Adapted from *Mod Pathol*. 2011;24:556–563.

is suspected, not all gastroenterologists follow the guidelines. All too frequently only specimens from the distal esophagus or the gastroesophageal junction are submitted with a requisition stating “rule out eosinophilic esophagitis.” If > 15 eosinophils/HPF are found in these locations only, one could state in a comment, “Although the histopathologic criteria for the diagnosis of eosinophilic esophagitis are met, reflux esophagitis may share similar features. Therefore, specimens from the more proximal esophagus may be helpful (or even necessary) to reach a more specific diagnosis.”

STOMACH

Normal Eosinophil Counts in the Gastric Mucosa

Although most observers consider the presence of a few eosinophils in the lamina propria common, the Updated Sydney System acknowledged that intraepithelial eosinophils in the gastric mucosa are always viewed as abnormal.³⁹ Until recently, the limited information available regarding the normal range of gastric mucosal eosinophils was derived from infrequent and often uncontrolled case series, isolated case reports, or brief sections in textbooks of GI pathology.^{40–52} In the Kalixanda study, Talley et al⁵¹ noted a mean eosinophil count of 11 eosinophils in 5 HPF in biopsies from the cardia, body, and antrum of asymptomatic adult volunteers from Northern Sweden. DeBrosse et al⁴⁴ found peak eosinophil counts of 8 eosinophils/HPF in antral and 11 in oxyntic mucosal biopsies from 19 children.

We recently enumerated eosinophils in the lamina propria of patients from a wide age range and geographic areas in the United States who had no known history of relevant GI disease, and whose gastric biopsies were diagnosed as unremarkable (Table 2).⁵³ The mean eosinophil count for 135 normal patients (age range, 4 to 81 y) was 4 eosinophils/HPF (± 4 SD), equivalent to 15 ± 17 SD eosinophils/mm² (range, 0 to 110). There were no significant differences between the counts in biopsies from the antrum and corpus, and no significant variation by either age or geographic location. Our findings were in essential agreement with those of both DeBrosse et al and Talley et al.^{44,51}

Causes of Gastric Mucosal Eosinophilia

Increased numbers of eosinophils in the lamina propria have been documented in infection with *Anisakis* spp.,⁵⁴ *Strongyloides stercoralis*,⁵⁵ *Helicobacter pylori* infection,^{56–58} post *H. pylori* treatment,⁵⁹ drugs,⁶⁰ Crohn disease,⁵³ pyloric obstruction,^{41,46} tumors,⁴⁹ connective tissue diseases, hematopoietic disorders, food allergy, and in patients with the rare eosinophil-associated GI disorders.^{61,62}

Eosinophilic Gastritis

Isolated (idiopathic) eosinophilic gastritis is a poorly characterized condition. Although rare cases have been reported sporadically through the literature,^{63–66} starting from the mid-1980s *H. pylori* virtually monopolized the efforts of gastric researchers, so the few cases or descriptions of eosinophilia in the gastric mucosa were believed to be related to either current or treated *H. pylori* infection.⁵⁹

Recently, we reported a series of 60 patients with gastric mucosal eosinophils counts between 50 and > 160 eosinophils/HPF (200 and > 600 eosinophils/mm²).⁵³ Epigastric pain was the most common reason for the endoscopy in both adults and children, followed by reflux and dysphagia. The most common endoscopic findings were a normal stomach or erythema and gastritis, with or without erosions. The histopathologic findings from our case series are described below and summarized in Table 3.

Practical Suggestions for Diagnosis

In eosinophilic gastritis, epithelial eosinophilic infiltration (Fig. 2A) is a very common finding, particularly if a sufficient number of sections are examined. Sheets of eosinophils (Fig. 2B) are seen in more than half of these patients' biopsies. Eosinophils tend to surround the foveolae and infiltrate the epithelium, but typically do not spill into the lumen to form eosinophilic “pit abscesses” (Fig. 2B). Involvement of the muscularis mucosae or submucosal tissue may be noted. Although reactive epithelial changes similar to those found in chemical gastropathy are common, neither foveolar hyperplasia nor intestinal metaplasia are characteristic.

TABLE 3. Pathologic Characterization of Eosinophilic Gastritis

Median density (eosinophils/HPF)	40
(Eosinophils/mm ²)	170
Mean density (eosinophils/HPF)	49
(Eosinophils/mm ²)	206
Range (eosinophils/HPF)	9-158
Range (eosinophils/mm ²)	40-665
Epithelial involvement	
Abundant	17
Rare	35
None	8
Eosinophils forming sheets	33
Muscularis mucosae involvement	26

Eosinophil counts and histologic characteristics from 60 patients with marked gastric mucosal eosinophilia. HPF indicates high-power field. Adapted from *Mod Pathol*. 2011;24:556–563.

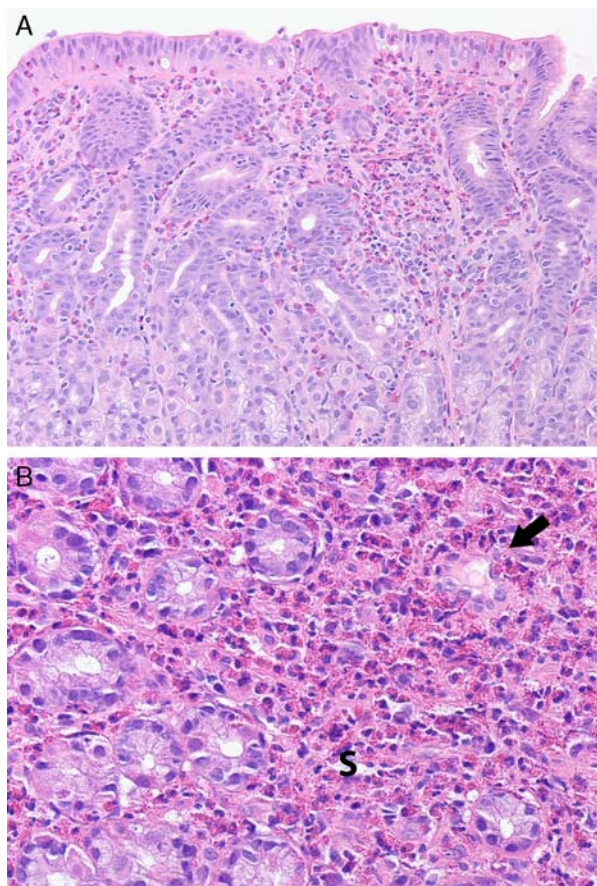


FIGURE 2. Eosinophilic gastritis. A, Gastric mucosa with marked eosinophilic infiltration within the lamina propria and eosinophils infiltrating both glands and superficial foveolar epithelium. B, Sheets (S) of eosinophils distort the gastric mucosal architecture and infiltrate a gastric pit (arrow).

We recommend that the term “histologic eosinophilic gastritis” be used for the diagnosis in patients who: (1) have gastric biopsies that show an average density ≥ 127 eosinophils/mm² (or ≥ 30 eosinophils/HPF on microscopes equipped with wide-lens oculars) in at least 5 separate HPFs; and (2) have no known associated cause of eosinophilia. If *H. pylori* organisms are detected, the diagnosis of eosinophilic gastritis can be established only if the mucosal eosinophilia persists several months after successful eradication.

In cases where regenerative epithelial changes are noted in a gastric biopsy with significant eosinophilic infiltrates that fall below the recommended quantitative threshold, we suggest a diagnosis of “reactive gastropathy with prominent eosinophils.” This diagnosis should include a comment mentioning the possibility of eosinophilic gastritis among other differential diagnoses deemed appropriate in the context of the patient’s clinical situation.⁵³

SMALL AND LARGE INTESTINE

Normal Eosinophil Counts in the Small and Large Intestinal Mucosa

Lymphocytes, plasma cells, eosinophils, and a limited number of macrophages and mast cells compose the normal

inflammatory component of the lamina propria in the small and large intestine. Although the histopathologic characteristics of lymphocytes in these regions have been studied extensively,⁶⁷ the quantity and quality of eosinophilic infiltration have not received the same attention. Although it is clear that the lamina propria of the normal small intestine contains eosinophils, a consensus has not been reached on the ranges of normal for the different segments of the small intestine. Rare intraepithelial eosinophils are considered normal in both the small and large intestine.⁶⁸

In the colon, eosinophils and other constituent inflammatory cells follow a decreasing gradient along the length of the colon, from proximal to distal.^{69,70} On account of this gradient, interpretation of eosinophilic density must be performed in the context of the anatomic site of the biopsy within the colon.⁷¹ Although several small studies have quantified the number eosinophils in each segment of the colon in healthy populations, with counts ranging from 10 to 70 eosinophils/HPF in the cecum to 1 to 30 in the rectum, no universally accepted normal range has been established.^{44,47,72} Reasons for the failure to achieve a consensus include topographic variability, reports of higher background counts in certain geographic regions, potential seasonal variation, and the participation of eosinophils in various nonspecific inflammatory response.^{73–75}

Causes of Small and Large Intestinal Eosinophilia

Intestinal eosinophilia, a term used here to describe a greater than usual number of eosinophils in the judgment of an experienced pathologist, has been associated with both systemic eosinophilic disorders (idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, and systemic mastocytosis), and noneosinophilic disorders such as parasitic infections, drug reactions, IBD, connective tissue disease, vasculitis, and malignancy.^{76,77} Many secondary causes of intestinal eosinophilia can be identified with careful histopathologic examination and correlation with clinical and laboratory data. Primary EGE, enteritis, or colitis can be diagnosed only after excluding all other known causes of eosinophilia.⁷⁶

Parasitic Infection

Small Intestine

Focal dense aggregates of eosinophils can be found in duodenal and proximal jejunal biopsies from patients with various helminthic infections, particularly adjacent to the worms, larvae, or eggs. As parts of the organism are often visible, the parasitic origin of the eosinophilic infiltrate is usually straightforward. However, only rarely is there a sufficient portion of the parasite in a tissue section to allow its taxonomic identification (Fig. 3A). Hookworms (*Ancylostoma caninum* and *Necator americanus*), pinworms (*Enterobius vermicularis*), *Eustoma rotundatum*, *Ascaris lumbricoides*, *Trichuris trichura*, *T. spiralis*, *Schistosoma* spp., and *Anisakis* spp., are among the helminths that can be found in the small intestine. Eosinophilic ascites has been reported in association with *Toxocara canis* and *S. stercoralis*.^{78,79} *Schistosoma* spp. eggs within “eosinophilic abscesses” are rarely found, and only in biopsy specimens from the terminal ileum. Often these eggs are also found in the colonic mucosa, making the diagnosis obvious.^{55,80–82}

A special case is represented by the infection with *A. caninum*, the dog hookworm, that may cause self-limited skin infection in humans (*larva migrans cutanea*).⁸³ In

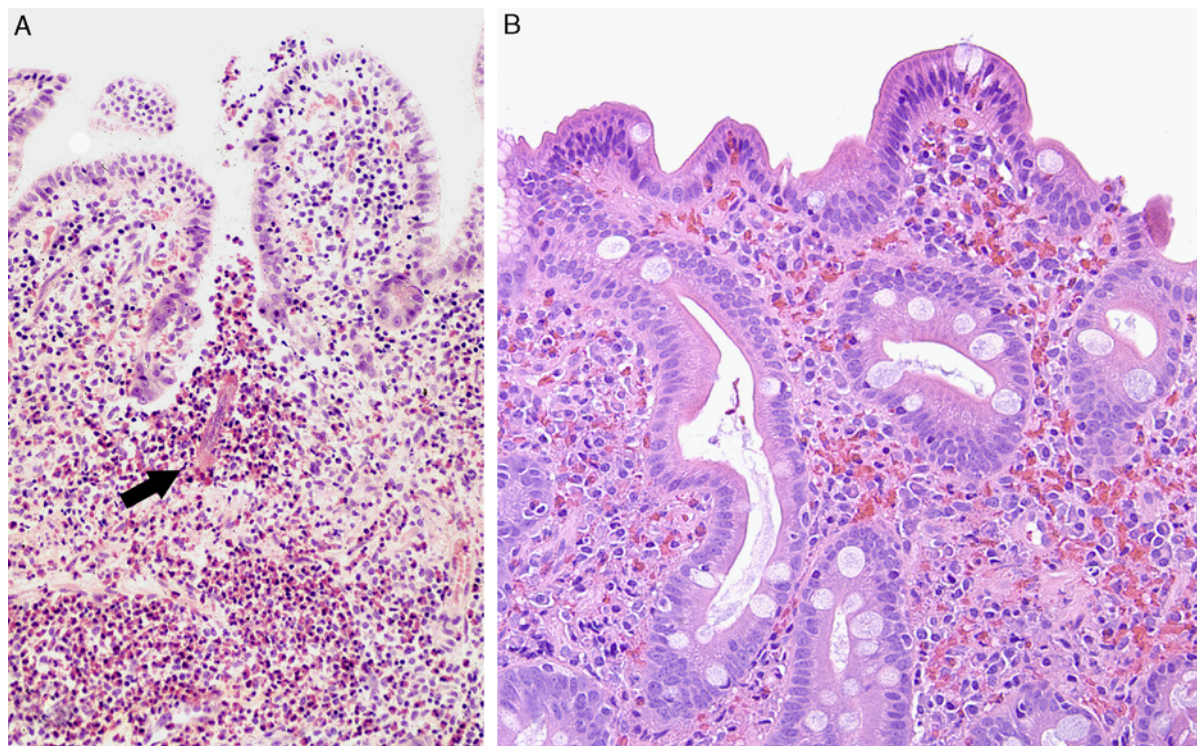


FIGURE 3. Eosinophilic enteritis. A, A portion of a parasitic organism is visible within a focus of dense eosinophilic inflammation. B, Small bowel mucosa with eosinophilic infiltration of the lamina propria and epithelium, degranulated eosinophils, and villous blunting.

certain parts of the world, notably the Northern Territory in Australia, a peculiar type of human enteritis caused by *A. caninum* has been described. Patients present with persistent, severe abdominal pain, and marked peripheral and mucosal eosinophilia in small intestinal biopsies.

Colon

Tissue-invading helminths elicit significant eosinophilic responses in the colonic mucosa. Thus, the detection of a dense focal eosinophilic infiltrate involving a few crypts and the intervening lamina propria (Fig. 4A) should prompt a search for helminthic larvae, such as *S. stercoralis* (Fig. 4B), *Schistosoma* spp. eggs (Fig. 4C),⁸⁴ or fragments of *Trichuris trichiura* (a colon-dwelling nematode that anchors itself to the mucosa by burying a portion of its cephalic end just under the superficial epithelium (Fig. 4D)).^{85,86} More rarely, *Angiostrongylus costaricensis*, and *Gnathostoma* spp. have been associated with colonic eosinophilia.^{87–89} Lumen-dwelling helminths, whether they have a tissue invading cycle (*Ascaris lumbricoides*, hookworms, and nonhuman parasites such as *A. caninum* or *Ascaris suum*)⁹⁰ or not (tapeworms, *Enterobius vermicularis*), are rarely implicated in eosinophilia of the colonic mucosa.^{91,92} With the possible exception of *Dientamoeba fragilis*, protozoa do not cause tissue eosinophilia.⁹³ Patient origin, residence, and travel history are important considerations when a parasitosis is suspected. If recognizable parasite forms are not detected, a generic diagnostic line such as “eosinophilic infiltrate possibly related to a parasitic infection” should be used. A comment suggesting stool examination and serological tests should also be included in a comment.

Drug Reactions

Although we are frequently tempted to ascribe unexplained eosinophilia (in tissues or in the peripheral blood) to the use of certain medications, implicating a drug as the cause of intestinal eosinophilia or other specific histopathologic change is challenging. A temporal clinico-pathologic correlation must be established between drug, onset of symptoms, and tissue eosinophilia. Resolution should be demonstrated when the drug is withdrawn and symptoms should reemerge when the patient is challenged with the medication. Histologic documentation of each phase would be ideal, but is generally not available.⁹⁴ Although case reports or small series have associated intestinal eosinophilia with a number of prescription medications (including clozapine, carbamazepine, enalapril, gemfibrozil, rifampicin, nonsteroidal anti-inflammatory agents, tacrolimus, and therapeutic gold compounds), several of these drugs are implicated on the basis of single cases, lacking detail, and confirmatory studies.^{72,95–104} In a small case series (27 patients), Casella et al⁷² associated colonic eosinophilia with nonsteroidal anti-inflammatory agents (nimesulide, diclofenac, and ibuprofen), antiplatelet agents (aspirin and ticlopidine), and estrogenic agents. The increased eosinophilic infiltrate was primarily localized to the left colon, supporting similar findings in previous studies.⁷⁷ Drug-induced colonic eosinophilia may, therefore, be suspected when the previously described temporal cause-effect relationship is observed and all other causes of colonic eosinophilia are excluded, particularly in the presence of the medications listed above. This diagnosis requires clinicopathologic correlation; hence, communication with the treating clinician is imperative.

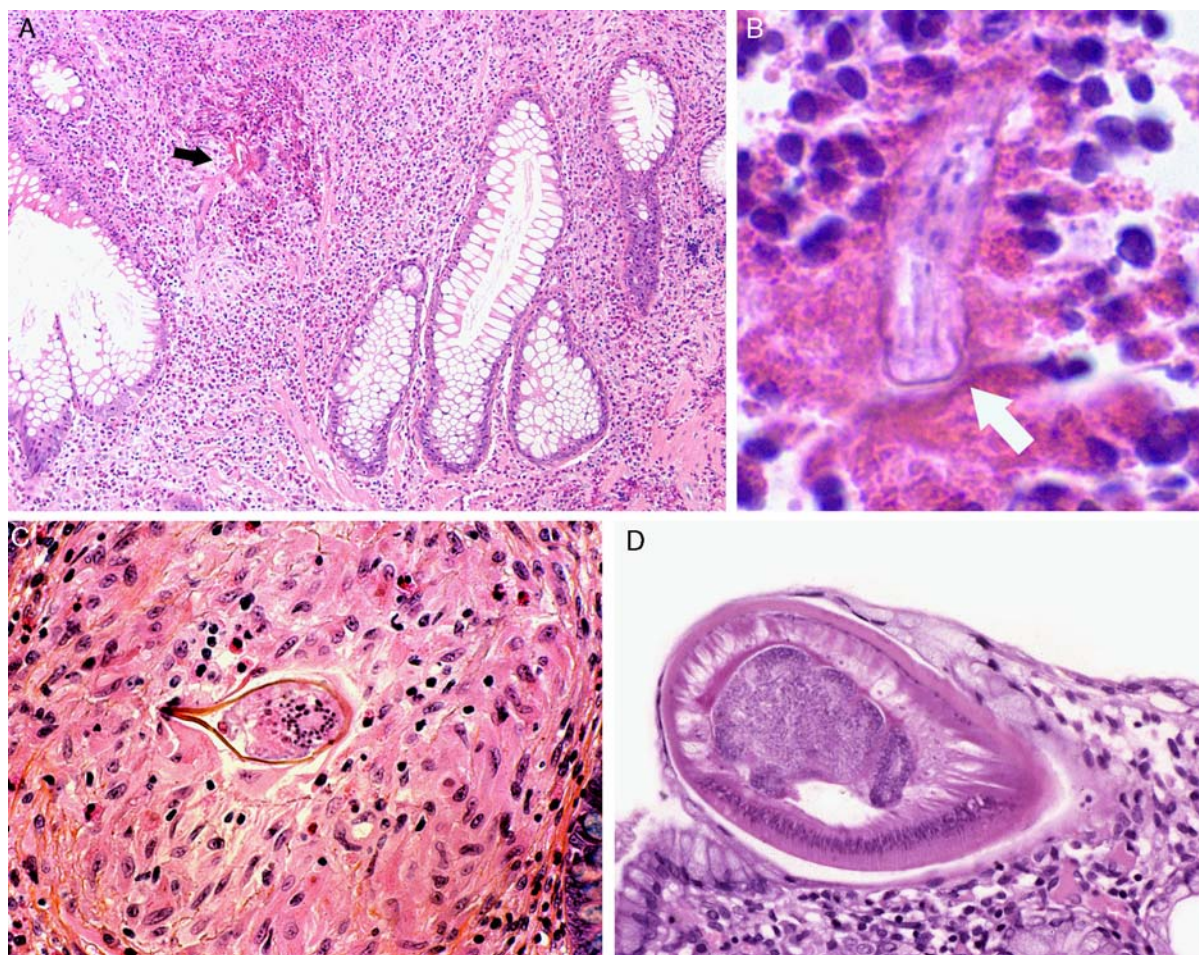


FIGURE 4. Parasitic infection. A, A dense aggregate of eosinophils surrounds fragments of a parasitic organism. B, *Strongyloides stercoralis*. C, *Schistosoma* spp. egg. D, *Trichuris trichiura*. (AFIP-69-7904). Arrows indicate parasitic organisms.

Inflammatory Bowel Disease

In both active and inactive ulcerative colitis and Crohn disease, eosinophils represent an important and often conspicuous component of the inflammatory response.^{105,106} However, neither sheets of eosinophils nor epithelial infiltration are usually evident in these patients. In addition, the diagnosis is usually suggested by the distorted mucosal architecture and the prominence of dense mixed inflammatory infiltrates (Figs. 5–7). Both the contribution of eosinophils to the pathogenesis of IBD and their prognostic significance in active and quiescent disease is in need of further elucidation. Recent studies suggest that eosinophils may have an important role in tissue destruction, resolution, and repair.¹⁰⁷ Whether eosinophilic activity predicts a better or worse outcome for the patient remains undetermined.

Connective Tissue Disease

Accumulations of eosinophils in the colon have been described in connective tissue diseases,^{108,109} and the extent and quality of the eosinophilic infiltrate may be revealing. For example, in scleroderma, dermatomyositis, and polymyositis, biopsies may reveal a band-like infiltrate of eosinophils and mast cells between the small intestinal crypts and the muscularis mucosae, and involvement of the deeper layers of the intestinal wall. Such histologic findings

should prompt a comment recommending ancillary studies for serum autoantibodies implicated in the above conditions, and evaluation for episodic peripheral eosinophilia.⁷⁹

Vasculitides

Churg-Strauss syndrome is a systemic necrotizing vasculitis characterized by asthma, blood hypereosinophilia, and eosinophil-rich granulomatous inflammation of the respiratory tract and extrapulmonary organs. The GI tract is affected in approximately 30% of the patients, with eosinophilic infiltration of the bowel wall and mesenteric vasculitis causing diarrhea, bleeding, obstructive nodular masses, peritonitis, ascites, ischemia, and perforation.¹¹⁰ Eosinophil-rich granulomas with necrosis involving medium to small sized vessels are characteristic histopathologic findings.⁷⁹

Polyarteritis nodosa, another systemic necrotizing inflammatory disease of small and medium-sized arteries, affects the GI tract in up to 25% of the patients. These patients develop inflammatory lesions that often involve branching points and bifurcations of arteries and lead to aneurysms, thrombosis, or rupture of the vessels. GI hemorrhage, infarction, and perforation are rare complications. Histologically, arteritis may be identified in a background of eosinophilic inflammation.¹¹¹

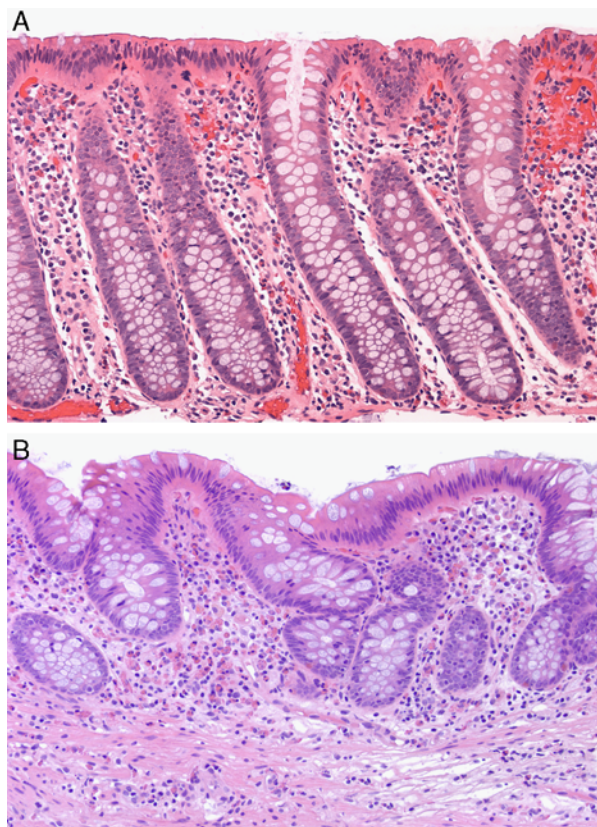


FIGURE 5. A, The normal inflammatory population of the lamina propria in the large intestine includes lymphocytes, plasma cells, eosinophils, and a limited number of macrophages and mast cells. B, Distorted mucosal architecture and a mixed inflammatory infiltrate with conspicuous eosinophils in a colon biopsy from a patient with inflammatory bowel disease.

Malignancies

Beside chronic eosinophilic leukemia and systemic mastocytosis (discussed below in The GI Tract in Systemic Eosinophilic Disorders), various malignancies may be associated with intestinal eosinophilia. A brisk eosinophilic response is occasionally observed in association with GI adenocarcinomas.⁷⁷ Massive tissue eosinophilia has also been reported in the stomach and small intestine in patients with malignant lymphoma. In these cases, although eosinophils were the predominant inflammatory cell type, plasma cells, epithelioid histiocytes, and lymphocytes were also present.¹¹² A single case of colonic eosinophilia has been reported as a possible paraneoplastic syndrome in a patient with low-grade marginal zone B-cell lymphoma.¹¹³ Rarely, graft-versus-host disease in bone marrow transplant patients has been associated with eosinophilic colitis.¹¹⁴

Primary Eosinophilic Enteritis

In the endoscopic investigation of the small intestine, biopsy specimens may be obtained from the duodenum, the first few centimeters of the jejunum, or the terminal ileum. To our knowledge, significant diffuse eosinophilic infiltration limited to the duodenum (eosinophilic duodenitis) has not been described. Pure isolated eosinophilic enteritis has been reported exceptionally, and only in the radiologic and surgical literature.^{115,116} In the overwhelming majority of

patients, increased mucosal eosinophils in the small intestine are accompanied by eosinophilia in other segments of the upper or lower GI tract and represent an expression of EGE.

Primary Eosinophilic Colitis

Idiopathic eosinophilia isolated to the colon occurs in allergic colitis of infancy (also known as the “dietary protein-induced proctocolitis of infancy syndrome”) and the more poorly characterized adolescent and adult allergic colitis. Both are diagnosed after exclusion of all other known causes of eosinophilia.⁷⁶ Allergic colitis in infancy results from immune-mediated reactions to ingested proteins, such as cow’s milk and soy proteins.^{76,117} Infants most often present with rectal bleeding and diarrhea within the first few months of life.¹¹⁷ Removal of causative allergens through dietary manipulation usually results in a complete response.^{76,117–120} Allergic colitis of infancy may be an early expression of food-protein-induced enterocolitis, a more severe disease that can produce diarrhea and vomiting in infants several hours after ingesting certain foods.^{76,121}

Primary eosinophilic colitis is rarely diagnosed in older children and adults.¹¹⁸ Similar to EGE, the natural history of the disease has not been well documented.⁷⁶ Studies in older children reported abdominal pain, diarrhea, constipation, and rectal bleeding as common presenting symptoms.¹²² Immunoglobulin E (IgE)-associated triggers are rarely identified, and the disease seems to be a chronic waxing and waning condition requiring management with anti-inflammatory agents, including aminosalicylates and systemic or topical glucocorticoids.^{76,121}

Histopathologic Features of Eosinophilic Colitis and Suggested Criteria

Increased number of mucosal and intraepithelial eosinophils with formation of eosinophil crypt abscesses, extensive degranulation, epithelial regenerative changes, and minimal active and chronic inflammation have been described as the key features in eosinophilic colitis (Table 4). If the disease has been long-standing, evidence of chronicity would not be unexpected.⁶⁸

In eosinophilic proctocolitis of infancy (a condition reported exclusively in young children), the overall architecture of the mucosa is well preserved and the eosinophilic infiltration is typically more localized to the rectum.^{68,76} It has been proposed that more than 60 eosinophils/10 HPFs in the lamina propria and eosinophilic infiltration in the epithelium or the muscularis mucosae are indicative of eosinophilic proctocolitis. Other findings may include peripheral blood eosinophilia (50%) and eosinophils in the stool.¹²¹

Primary Eosinophilic Gastroenteritis

In 1937, Kaijser¹²³ first described a condition characterized by patchy or diffuse eosinophilic infiltration of GI tissue, which was later named EGE. Patients with this uncommon condition present with a wide range of GI manifestations, focal or diffuse eosinophilic infiltration of the GI wall, and no evidence of a disease process known to cause intestinal eosinophilia (hence the designation of “primary”).¹²⁴ The majority of patients are diagnosed between the third and fifth decade (although EGE has been reported in all age groups),¹²⁵ and present with a wide range of clinical manifestations, including abdominal pain,

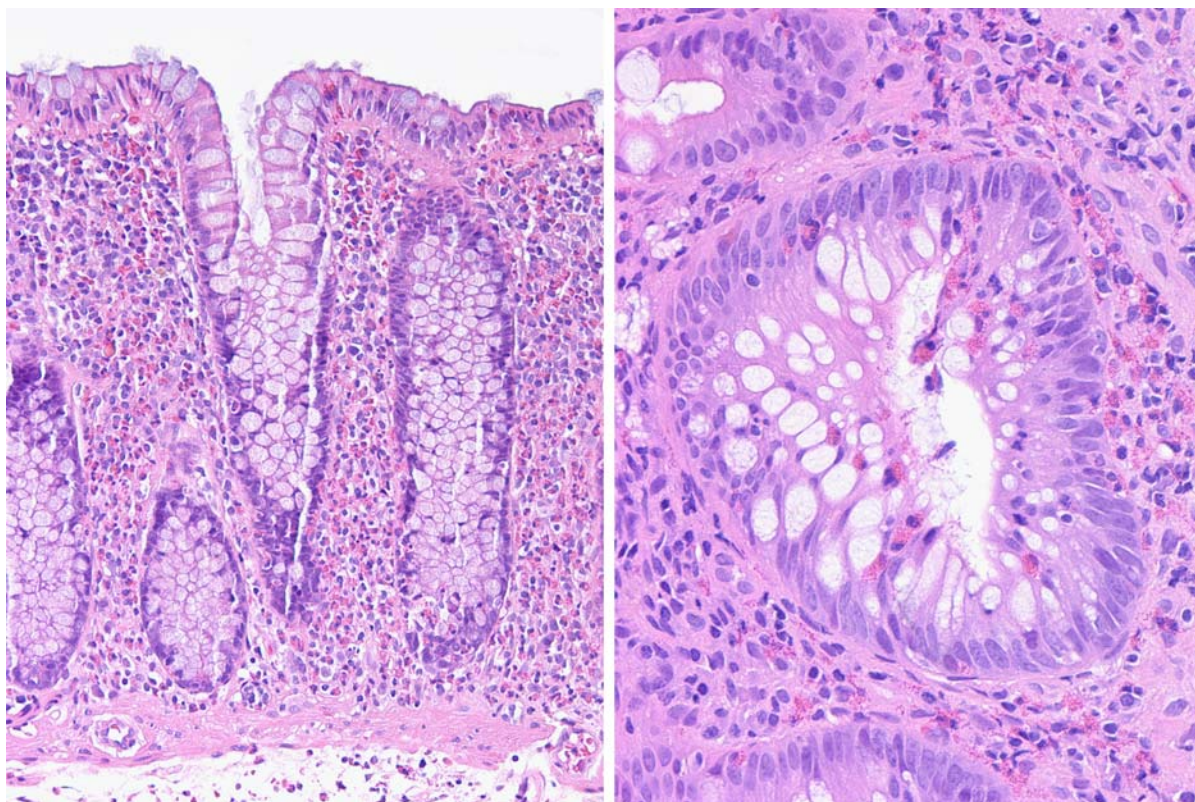


FIGURE 6. Eosinophilic colitis. Colonic mucosa with increased eosinophils and additional pathologic features of injury including degranulated eosinophils, intraepithelial eosinophils, and epithelial regenerative changes.

nausea, vomiting, diarrhea, and weight loss.^{121,124,126} The stomach and small intestine are the most frequently affected segments of the gut.¹²⁵ Tissue eosinophilia is often patchy and may involve any portion and any layer of the GI tract (mucosa, muscularis propria, or serosa) with different intensity. Interesting but not surprisingly, the degree of involvement of each layer determines, to an extent, the clinical manifestations. When the infiltration is predominantly mucosal (the most common type of EGE in recent years),¹²⁷ manifestations include protein-losing enteropathy, malabsorption, GI bleeding, and iron deficiency anemia. Stricture, ulcers, or obstruction are more common when the muscular layer is involved^{128,129}; whereas eosinophilic ascites is characteristic of serosal disease.^{126,130,131} Imaging studies may reveal variable nonspecific abnormalities such as bowel wall thickening, prominent mucosal folds, luminal narrowing, or ascites.^{78,132} Nonspecific endoscopic findings have also been described including hyperemic mucosa, friability, ulcerations, erosions, nodules, and loss of vascularity.^{78,133}

Although the pathogenesis of EGE has not been completely elucidated, an allergic component is supported by several observations: 10% of patients with EGE have an immediate family member with a similar condition,⁶¹ approximately 75% of patients are atopic,^{134,135} the severity of disease can sometimes be reversed by an allergen-free diet,¹³⁶ and mast cell degranulation is commonly found in tissue specimens.^{121,137} Unlike patients with eosinophilic esophagitis, the majority of those with EGE have increased serum total IgE and food-specific IgE levels, and positive skin test responses to a variety of food antigens. Peripheral

eosinophilia has been reported in the majority of EGE patients.¹²⁴ The diagnosis is commonly reached when biopsies obtained for the evaluation of a chronic gastroenteritis-like syndrome show a marked eosinophilic infiltrate.

The long-term course of EGE is not well characterized, but it seems to be a chronic condition. Traditionally, treatment options for EGE include elimination or elemental diets and corticosteroids. More recently LTD4 (leukotriene) receptor antagonists and antibodies against IL-5 or eotaxin have been studied.^{76,121,127}

Histopathologic Features of Eosinophilic Gastroenteritis and Suggested Criteria

Although there are no established diagnostic criteria to determine what density or distribution mucosal eosinophils constitutes a pathologic process,¹³⁸ a benchmark of more than 20 eosinophils/HPF has been suggested when the clinical history is consistent with EGE.¹²⁶ The great variability of eosinophil counts in different parts of the GI tract suggests such a general arbitrary upper limit of normal seems ill-advised. In a recent review, Collins⁶⁸ has taken a more sensible position, suggesting less emphasis on eosinophil quantity and focusing more on additional pathologic changes. She also suggested using the term “mucosal eosinophilia” to describe increased numbers of mucosal eosinophils without other histologic alterations, and reserving the term “EGE/colitis” for cases with additional pathologic changes. Examples of such findings, summarized in Table 4, include degranulated eosinophils,

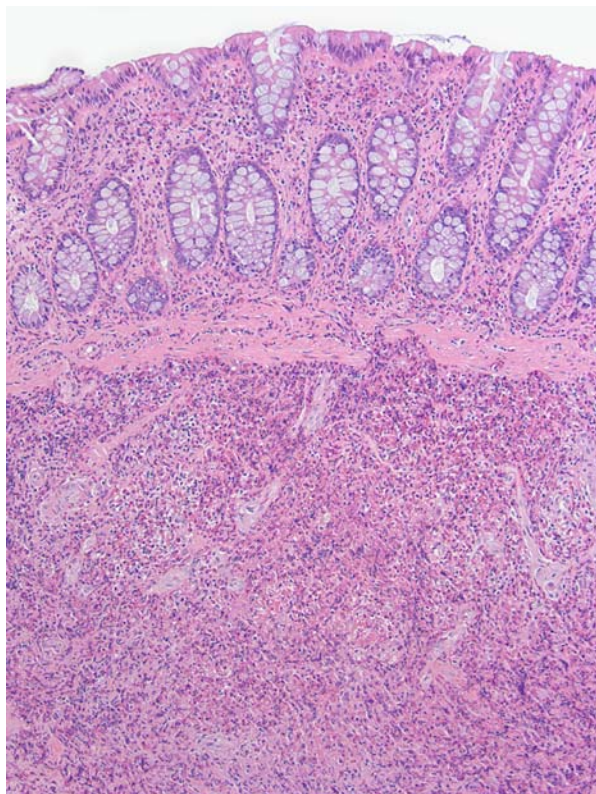


FIGURE 7. Eosinophilic gastroenteritis. Markedly increased eosinophilic infiltration of the mucosa, *muscularis mucosae* and submucosa.

intraepithelial eosinophils, eosinophil crypt abscesses, epithelial degenerative and regenerative changes, villous atrophy in the small bowel (Fig. 3B), or eosinophils in the muscularis mucosae, submucosa, or both.⁶⁸ It must be emphasized, however, that if the eosinophilic infiltrates are confined predominantly to the submucosa or serosa, mucosal biopsies may be noncontributory. In these patients, a full-thickness surgical biopsy may be necessary if justified by a high index of suspicion derived from clinical and radiologic evidence.^{124,131,139} In research settings, the

TABLE 4. Histopathologic Findings Suggestive of Eosinophilic Gastroenteritis/Colitis

Increased number of mucosal eosinophils (subjective, no absolute quantitative threshold is defined)
Degranulated eosinophils
Intraepithelial eosinophils
Eosinophil gland/crypt abscesses
Epithelial degenerative and regenerative changes
Foveolar/crypt hyperplasia
Villous atrophy in the small bowel
Minimal acute and chronic inflammation
Eosinophils in <i>muscularis mucosae</i> or submucosa

If secondary causes of eosinophilia have been ruled out, increased eosinophils in the presence of some or all of the above pathologic features suggests primary eosinophilic gastrointestinal disease. "Mucosal eosinophilia" is recommended if there are no pathologic changes beyond increased eosinophils. Adapted from *Immunol Allergy Clin North Am*. 2009;29:109–xi.

intensity of eosinophil degranulation, which has been correlated with disease severity, can be highlighted using a monoclonal antibody against human eosinophilic MBP.^{29,140}

The GI Tract in Systemic Eosinophilic Disorders

Eosinophil-associated enteritis and colitis may be the manifestation of systemic diseases, such as idiopathic hyper-eosinophilic syndrome, chronic eosinophilic leukemia, systemic mastocytosis, and other hematopoietic disorders.^{141,142} The idiopathic hypereosinophilic syndrome is defined by 3 diagnostic criteria: (1) marked peripheral eosinophilia exceeding 1,500 cells/ μ L persisting for longer than 6 months with no identifiable cause; (2) signs and symptoms of organ dysfunction mediated by intense eosinophilic infiltration; and (3) and no evidence of clonality. The target organ varies in different patients, with involvement of skin, heart, lungs, and central and peripheral nervous systems in more than 50% of cases.^{79,143,144} Chronic eosinophilic leukemia has a similar presentation, but the diagnosis requires features indicative of leukemia, such as increased blast cells, or evidence of eosinophil precursor clonality.^{145,146}

Systemic mastocytosis encompasses a heterogeneous group of myeloproliferative neoplasms of the mast cell and its precursors in which clonally derived mast cells infiltrate various tissues, including bone marrow, skin, the GI tract, liver, and spleen. Abdominal pain is the most common symptom, followed by diarrhea, nausea, and vomiting.¹⁴⁷ Gastrointestinal involvement includes microscopic infiltration of the liver, pancreas, and intestines by mast cells, which can be recognized by their spindle-shaped nucleus and fine eosinophilic granules. These mast cell granules contain chemotactic mediators that attract eosinophils into the tissues. Therefore, mast cell infiltrates can be masked by a concomitant increase in eosinophils.¹⁴⁸

I SEE TOO MANY EOSINOPHILS: NOW WHAT? PRACTICAL SUGGESTIONS FOR THE PATHOLOGIST

Neither clinical guidelines nor histopathologic criteria have been published for any of the conditions described in this review, with the exception of eosinophilic esophagitis. Even for this condition, the distinction from reflux esophagitis often remains elusive.

Therefore, in the absence of well defined diagnostic categories to which we can assign our cases of mucosal biopsies with increased eosinophils, what are we to do? Clinicians have little patience for inconclusive descriptive diagnoses followed by a catalog of differentials listing what can be found in any textbook. In an attempt to avoid being generic, some pathologists go through the consecrated rituals of deeper sections and special stains. The chances of finding a diagnostic fragment of parasite at the end of the paraffin ribbon are low, yet in gastric and intestinal biopsies it may be worth the minimal expense and the short delay. It is difficult to think of other surprises buried in the paraffin block that could explain mucosal eosinophilia.

Although immunostains against the eosinophil MBP are available, they have little use outside the research context: seeing dark brown instead of red granules can hardly help the incidental user narrow down a diagnosis. The temptation to stain for tryptase to highlight mast cells should also be carefully considered, in the context of the clinical scenario.

Old-fashioned histopathology and a good interaction with the clinician are more likely to help reaching a diagnosis than additional stains and tests. Epithelial damage, intercellular edema, regenerating epithelial cells, accompanying inflammatory cells, sloughing or ulceration, and architectural changes can reliably guide the pathologist through the maze of histologic possibilities. Furthermore, a succinct but relevant review of the clinical history including any information about allergy or atopy, current or recent medications (including nonprescribed home remedies), and the geographic history (patient's origin and recent travel) can help focus on certain diagnostic options. Pertinent laboratory data, including peripheral eosinophilia and serum IgE immunoglobulin levels, should be investigated. The endoscopic report and any previous biopsies should also be reviewed.

One of the reasons for the current state of uncertainty in the eosinophilic diseases of the GI tract is probably histopathologic underreporting. Uncertain of how to label a case, a pathologist may simply decide to ignore the increased eosinophils, ascribe the infiltrate to nonsteroidal anti-inflammatory drugs use, or relegate the information to a comment. Such practices may escape the attention of the clinician, and detection and the discovery of potentially important clinicopathologic relationships may be delayed. With the assistance of these practical tips, pathologists should now be able to recognize and report pertinent eosinophilic infiltrates in luminal GI biopsies and to better define and characterize these eosinophilic conditions.

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