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### Authors

Yu, Weibo

Wang, Hanlin L

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# Eosinophilic and mastocytic gastrointestinal diseases: current knowledge and controversy in histopathologic diagnosis

Weibo Yu, Hanlin L. Wang

Department of Pathology and Laboratory Medicine, David Geffen School of Medicine and Ronald Reagan Medical Center, University of California at Los Angeles, Los Angeles, CA, USA

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**Correspondence to:** Hanlin L. Wang, MD, PhD. Department of Pathology and Laboratory Medicine, David Geffen School of Medicine and Ronald Reagan Medical Center, University of California at Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA. Email: hanlinwang@mednet.ucla.edu.

**Abstract:** Eosinophilic and mastocytic gastrointestinal (GI) diseases represent a spectrum of immune-mediated inflammatory disorders characterized by abnormal accumulation of eosinophils or mast cells in the GI tract. This review summarizes current knowledge on epidemiology, pathogenesis, histopathologic features, diagnostic challenges, and ongoing controversies across three major domains: eosinophilic esophagitis (EoE), non-EoE eosinophilic gastrointestinal diseases (EGID), and mastocytic GI diseases. Although these entities are increasingly recognized in clinical practice, their diagnosis remains challenging because clinical manifestations are often nonspecific and overlap with other inflammatory and functional GI disorders. Consequently, substantial uncertainties persist regarding diagnostic criteria and clinical relevance of certain histologic patterns. For non-EoE EGIDs, histologic diagnosis is particularly complicated by wide regional variation in normal eosinophil densities, the lack of universally accepted diagnostic cutoffs in adults, and limited correlation between tissue eosinophil burden and symptom severity. In mastocytic GI diseases, additional challenges include distinguishing reactive mast cell hyperplasia from clonal mastocytosis and interpreting proposed entities such as mastocytic enterocolitis, whose clinical significance remains controversial. Given these limitations, histopathologic evaluation of GI biopsies plays a central role in disease recognition and classification. This review emphasizes practical aspects of tissue interpretation, including site-specific reference ranges, proposed diagnostic thresholds, characteristic morphologic patterns, ancillary immunohistochemical and molecular studies, and common interpretive pitfalls encountered in routine practice. Recognizing these diseases ultimately requires careful clinicopathologic correlation, integrating histologic findings with clinical, endoscopic, and molecular data. Improved standardization of diagnostic criteria and clearer definition of histologic thresholds remain critical unmet needs for both pathologists and clinicians managing these complex disorders.

**Keywords:** Eosinophilic esophagitis (EoE); eosinophilic gastrointestinal diseases (EGIDs); mastocytic gastrointestinal diseases (mastocytic GI diseases); mastocytosis

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## Introduction

Eosinophilic and mastocytic gastrointestinal (GI) diseases are a heterogeneous group of immune-mediated inflammatory disorders that have gained attention in both

clinical gastroenterology and pathology over the past two decades. These conditions are now recognized as significant contributors to chronic GI symptoms such as dysphagia, abdominal pain, diarrhea, and food impaction (1-3). The

eosinophils and mast cells are integral components of the GI immune system, participating in host defense, tissue homeostasis, and allergic inflammation (4-6). However, in pathologic states, dysregulated accumulation and activation of these cells can lead to tissue damage, fibrosis, and altered GI motility.

Despite advances in understanding disease mechanisms, the diagnosis of eosinophilic and mastocytic GI disorders remains challenging and, in many cases, controversial, largely because clinical manifestations are nonspecific and overlap with a wide range of inflammatory and functional conditions. As a result, histopathologic evaluation of GI biopsies plays a central role in diagnosis, often serving as the primary basis for disease classification, exclusion of secondary causes, and clinical decision-making. Nevertheless, significant uncertainties persist regarding the distinction between physiologic and pathologic cell densities, the interpretation of borderline or atypical histologic findings, and the clinical significance of certain proposed disease entities. Accordingly, this review mainly focuses on current knowledge and ongoing controversies in the histopathologic diagnosis of eosinophilic and mastocytic GI diseases.

## Eosinophilic esophagitis (EoE)

### *Introduction and epidemiology*

EoE can occur as an isolated disease or as part of the broader spectrum of eosinophilic gastrointestinal diseases (EGID) (7). In isolated EoE cases, the eosinophil-predominant inflammation is limited to esophagus, causing symptoms such as dysphagia, chest pain, and food impaction.

EoE was once considered as a rare condition, but now, it has emerged as one of the most frequent causes of dysphagia and food impaction in both pediatric and adult populations. A systematic review and meta-analysis in 2023, which analyzed 40 population-based studies from 15 countries, reported a pooled global incidence of 5.31 cases per 100,000 person-years and a prevalence of 40.04 cases per 100,000 inhabitants. Among them, the highest incidences were observed in high-income countries and the disease demonstrated a male predominance with an approximate male-to-female ratio of 3:1 (8).

The clinical presentation can differ depending on the patient's age. In children, EoE often manifests as feeding difficulties, vomiting, or abdominal pain, while

in adolescents and adults, dysphagia and recurrent food impactions predominate. The disease is strongly associated with atopic conditions such as asthma, allergic rhinitis, atopic dermatitis, and immunoglobulin E (IgE)-mediated food allergy (9,10). Furthermore, epidemiologic studies have demonstrated an increased risk in patients with inflammatory bowel disease, with a meta-analysis showing an almost four-fold increase in the odds of EoE in patients with inflammatory bowel disease compared to the general population (11). In addition, patients with EoE may develop adaptive behaviors, such as excessively chewing, increased fluid intake with meals, food modification, and social avoidance, to cope with swallowing difficulties. Recent studies indicate that these adaptive behaviors are associated with active EoE and may be a clinical marker of histologic disease activity (12).

### *Pathogenesis*

EoE develops through a complex interaction of genetic predisposition, environmental factors, and immune dysregulation. It is driven by an antigen-mediated, Th2-polarized immune response that is most often triggered by food allergens (13). Genome-wide association studies have identified multiple susceptibility loci, including *TSLP*/*WDR36*, *CAPN14*, *LRRC32-C11orf30*, and *STAT6*, with *CAPN14* being particularly noteworthy for its esophagus-specific expression and role in epithelial remodeling under inflammatory conditions (14,15).

Histologic and molecular studies have also demonstrated epithelial barrier dysfunction in EoE, characterized by dilated intercellular spaces, decreased expression of barrier proteins such as filaggrin and desmoglein-1, and infiltration by eosinophils, mast cells, and Th2 lymphocytes (16,17). Cytokines play an important role in EoE pathogenesis. For example, interleukin (IL)-5 promotes eosinophil proliferation and survival, while IL-13 induces transcriptional changes in epithelial cells that impair barrier function and perpetuate inflammation (18,19). Clinically, although EoE frequently occurs in patients with other allergic disorders, the inflammatory mechanism is largely non-IgE-mediated, which explains the limited predictive value of skin testing for food triggers (13).

### *Histologic diagnosis*

From a pathologist's perspective, the diagnosis of EoE requires three elements: symptoms of esophageal dysfunction,

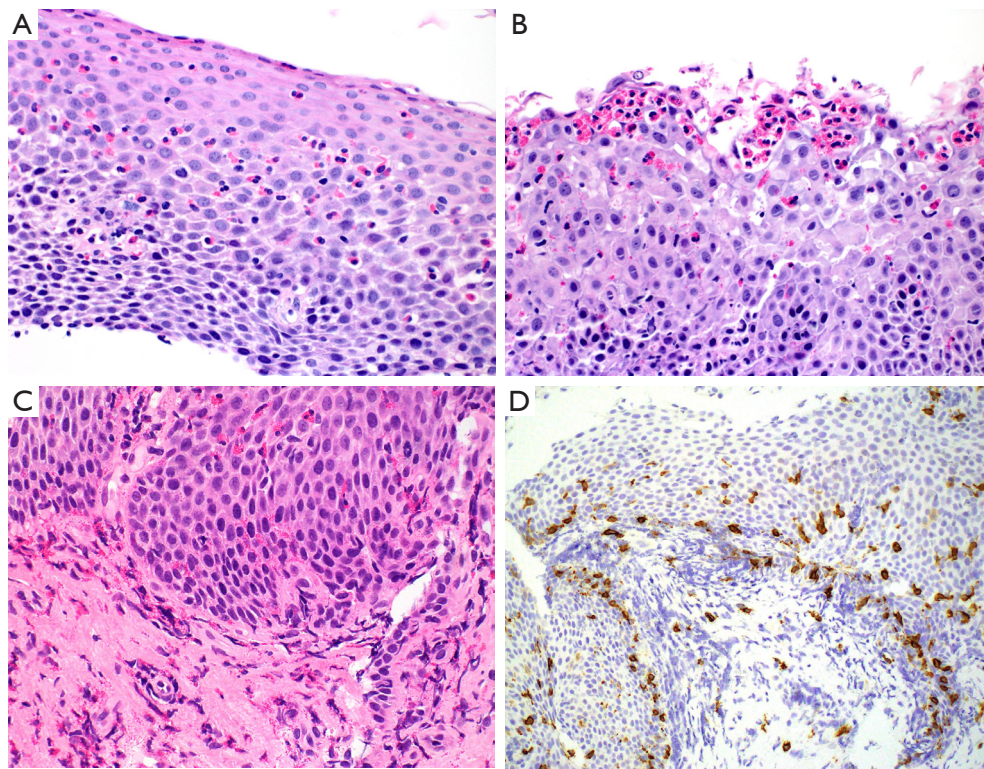


**Figure 1** Eosinophilic esophagitis. (A) An increased number of intraepithelial eosinophils, accompanied by basal cell hyperplasia and spongiosis (hematoxylin-eosin stain, original magnification  $\times 400$ ). (B) Eosinophilic microabscesses (hematoxylin-eosin stain, original magnification  $\times 400$ ). (C) Lamina propria fibrosis. Note the presence of eosinophils in fibrotic lamina propria (hematoxylin-eosin stain, original magnification  $\times 400$ ). (D) An increased number of mast cells in squamous epithelium and lamina propria (CD117 immunostaining, original magnification  $\times 200$ ).

a peak density of at least 15 eosinophils per high-power field (eos/hpf) in at least one esophageal biopsy, and exclusion of other causes of esophageal eosinophilia (20-22). Given the patchy nature of the disease, optimal sampling requires at least five biopsies taken from both the proximal and distal esophagus (23).

At low magnification, histologic examination often reveals marked basal zone hyperplasia of the squamous epithelium involving more than one-third of the epithelial thickness, elongation of vascular papillae extending beyond the mid-epithelium, and surface irregularities that may include parakeratosis or focal erosions. Spongiosis, characterized by dilated intercellular spaces due to intercellular edema, may be visible as a pale, reticular change and reflects epithelial barrier dysfunction (24).

When viewed under higher magnification, the defining feature is a widespread infiltration of eosinophils within the squamous epithelium (*Figure 1A*), often more concentrated

near the surface. Clusters of four or more eosinophils along the luminal edge, known as eosinophilic microabscesses, may be seen (*Figure 1B*). Signs of eosinophil degranulation, seen as bright, eosinophilic granules scattered outside the cells, may indicate active inflammation. In long-standing disease, fibrosis may develop in the lamina propria, which can be easily recognized on routine hematoxylin and eosin (H&E) staining (*Figure 1C*) but is best demonstrated with trichrome staining. Eosinophils may be present in fibrotic lamina propria. Mast cells are often increased in number, which can be identified with CD117 or tryptase immunohistochemistry and are believed to play a role in tissue remodeling (*Figure 1D*). Features of remodeling, including basal zone hyperplasia, elongation of the papillae, lamina propria fibrosis, and ongoing spongiosis, are particularly important in cases of “EoE without eosinophils”, where inflammation is minimal but structural changes remain (22).

**Table 1** Eosinophilic esophagitis histology scoring system

| Histologic features           | Grade (severity) scores                                                                                                                                                                                                | Stage (extent) scores                                                                                                                                                           |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eosinophilic inflammation     | 0: intraepithelial eosinophils not present; 1: PEC <15/hpf; 2: PEC 15–59/hpf; 3: PEC >60/hpf                                                                                                                           | 0: intraepithelial eosinophils 0–14/hpf; 1: PEC ≥15/hpf in <33% of hpfs; 2: PEC ≥15/hpf in 33–66% of hpfs; 3: PEC ≥15/hpf in >66% of hpfs                                       |
| Epithelial basal zone         | 0: not present; 1: occupies >15% but <33% of total epithelial thickness; 2: occupies 33–66% of total epithelial thickness; 3: occupies >66% of total epithelial thickness                                              | 0: not present; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium                                     |
| Eosinophil abscess            | 0: groups or aggregates of eosinophils not present; 1: group of 4–9 eosinophils; 2: group of 10–20 eosinophils; 3: group of >20 eosinophils                                                                            | 0: groups or aggregates of eosinophils not present; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium |
| Eosinophil surface layering   | 0: absent (fewer than 3 aligned eosinophils); 1: layering of 3–4 eosinophils; 2: layering of 5–10 eosinophils; 3: layering of >10 eosinophils                                                                          | 0: absent; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium                                          |
| Dilated intercellular spaces  | 0: not seen at any magnification; 1: intercellular bridges visible at ×400 magnification only; 2: intercellular bridges visible at ×200 magnification; 3: intercellular bridges visible at ×100 magnification or lower | 0: not seen at any magnification; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium                   |
| SEA                           | 0: not present; 1: SEA without eosinophils; 2: SEA with any eosinophils; 3: shed altered surface epithelium admixed with numerous eosinophils consistent with exudate                                                  | 0: not present; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium                                     |
| Dyskeratotic epithelial cells | 0: not present; 1: 1 cell/hpf; 2: 2–5 cells/hpf; 3: >5 cells/hpf                                                                                                                                                       | 0: not present; 1: (any grade >0) in <33% of epithelium; 2: (any grade >0) in 33–66% of epithelium; 3: (any grade >0) in >66% of epithelium                                     |
| Lamina propria fibrosis       | 0: not present; 1: fibers are cohesive and interfiber spaces cannot be demarcated; 2: fiber diameter equals the diameter of a basal cell nucleus; 3: fiber diameter exceeds the diameter of a basal cell nucleus       | 0: not present; 1: (any grade >0) in <33% of lamina propria; 2: (any grade >0) in 33–66% of lamina propria; 3: (any grade >0) in >66% of lamina propria                         |

This table was adapted from the article by Collins *et al.* (25) with the permission from Oxford University Press. hpf, high power field; PEC, peak eosinophil count; SEA, surface epithelial alteration.

### Histologic scoring systems

Although the peak eosinophil count is central to diagnosis, it does not capture the full histologic spectrum of EoE. The Eosinophilic Esophagitis Histology Scoring System (EoE-HSS) was developed to assess both the severity (grade) and the extent (stage) of multiple features, including eosinophil density, microabscesses, surface layering, basal zone hyperplasia, dilated intercellular spaces, and lamina propria fibrosis (*Table 1*) (25). There is evidence to show that this scoring system is reproducible and correlates with global assessments of histologic severity and with responsiveness to therapy (26).

The EoE Histologic Remission Score (EoEHRS) based on EoE-HSS evaluation offers a standardized approach to defining histologic remission, requiring a peak eosinophil

count of less than 15 eos/hpf at all sites along with low cumulative grades for other histologic features in both proximal and distal biopsies (27). Prospective data suggest that a more stringent threshold of less than 5 eos/hpf may be a better predictor of complete clinicopathologic remission (28). Currently, these thresholds are not universally adopted. The validation and routine adoption of histologic scoring systems such as the EoEHRS remain important goals for future research.

### Differential diagnosis

Esophageal eosinophilia is not specific to EoE, and a variety of other conditions must be considered for differential diagnoses. Gastroesophageal reflux disease (GERD) remains the most common alternative diagnosis. In GERD,

**Table 2** Classification of eosinophilic gastroenteritis

| Type    | Clinical characteristics                                        | Pathology                                                                                                                |
|---------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Mucosal | Diarrhea; GI bleeding; protein-losing enteropathy               | Increased numbers of intramucosal eosinophils; eosinophilic cryptitis and crypt abscesses                                |
| Mural   | Abdominal pain; bowel obstruction; nausea and vomiting          | Wall thickening; eosinophilic infiltrates in muscularis propria; destruction of muscularis propria; mucosa may be normal |
| Serosal | Abdominal pain; bowel obstruction; ascites; nausea and vomiting | Eosinophils limited to the serosa and subserosa; ascitic fluid with abundant eosinophils                                 |

GI, gastrointestinal.

eosinophilia is typically milder, with fewer than 10 eos/hpf, and shows a distal-predominant distribution, often without microabscess formation as seen in EoE. EGID beyond the esophagus, such as eosinophilic gastritis or enteritis, may involve the esophagus and present with similar histologic findings (29). Crohn disease can rarely involve the esophagus, usually in association with granulomatous and/or transmural inflammation. Connective tissue diseases such as systemic sclerosis may be associated with secondary esophageal eosinophilia. Certain medications, including bisphosphonates and doxycycline, can cause drug-induced esophagitis with eosinophils. Infectious esophagitis due to *Candida*, herpes simplex virus, or parasites can occasionally produce surface eosinophilia; in such cases, careful search for organisms is essential. EoE variants, such as EoE-like esophagitis, lymphocytic esophagitis, and mast cell-predominant esophagitis, may share molecular signatures with classic EoE and have the potential to progress to the full histologic phenotype (22).

### Controversies and evolving concepts

Several challenges complicate the clinical and histopathologic diagnosis of EoE. One is the concept of proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE), which was once regarded as a separate entity but is now recognized as clinically, histologically, and molecularly indistinguishable from EoE. Current consensus guidelines emphasize that a positive response to PPI therapy should not be used to exclude the diagnosis of EoE (30).

Another area of discussion is the potential mechanistic overlap between GERD and EoE. It has been proposed that acid reflux may impair epithelial barrier integrity, thereby facilitating allergen penetration and eosinophilic inflammation, while EoE-related subepithelial fibrosis could impair motility and worsen reflux symptoms (31).

The entity sometimes referred to as “EoE without eosinophils” describes patients who meet the clinical and, in some cases, molecular criteria for EoE but who do not meet the histologic threshold of 15 eos/hpf. This presentation may represent an early inflammatory phase or a late fibrostenotic stage in which active inflammation has subsided. In such cases, the presence of chronic remodeling changes may be the primary histologic clue (22).

Technological advances in digital pathology also bring additional considerations. Whole-slide imaging eliminates the traditional concept of the high-power field, making it essential to standardize eosinophil counts to a defined measurement area, such as 0.3 mm<sup>2</sup>, to avoid inter-laboratory variability (32).

## EGIDs

### Introduction

EGIDs encompass a group of inflammatory diseases characterized by prominent tissue eosinophilia in the GI tract, together with related symptoms and the absence of secondary causes. The spectrum includes EoE, gastritis, gastroenteritis, enteritis, and colitis. Eosinophilic gastroenteritis (EGE), first described by Kaijser in 1937 (33), most often involves the stomach and small intestine but may affect any segment from the esophagus to the rectum. Klein and colleagues, in a landmark 1970 article, divided EGE into three forms according to the depth of eosinophil infiltration: mucosal, mural, and serosal, each correlating with different clinical manifestations (*Table 2*) (34). For pathologists, the central difficulties lie in deciding when eosinophil numbers truly exceed the physiologic upper range, recognizing that inflammation may be discontinuous, integrating histologic features into the patient's broader clinical presentation, and confidently excluding secondary causes.

### Epidemiology

Although EGE is considered rare, its true incidence is uncertain and may be underestimated. In the United States, prevalence estimates range from 2.5 to 28 per 100,000 population, depending on the definitions applied (35,36). Another analysis placed the prevalence at 5.1 per 100,000, with a female predominance and higher rates in Caucasians (37). In a recent multicenter Dutch study, non-EoE EGIDs comprised roughly 2% of symptomatic patients undergoing endoscopic biopsy (38). Geographic variation may also be relevant to histologic interpretation. For example, normal mucosal eosinophil counts are significantly lower in Japanese adults than in North American populations (39). However, regardless of geographic location, non-EoE EGIDs remain likely underdiagnosed due to nonspecific symptoms, variable biopsy practices, and limited awareness among clinicians and pathologists (40).

### Pathogenesis

EGE arises from a complex interplay of immune mechanisms, frequently dominated by a Th2-type immune response to food or environmental antigens. Cytokines such as IL-4, IL-5, and IL-13, along with chemokines including eotaxin-1 and eotaxin-3, promote eosinophil recruitment and activation. Epithelial-derived cytokines such as thymic stromal lymphopoietin further shape the inflammatory milieu (41,42). As seen in EoE, mast cells are frequently increased in affected mucosa, and bidirectional interactions between mast cells and eosinophils may intensify tissue injury (43).

Molecular studies have identified disease-specific transcriptional patterns. For example, Shoda and colleagues reported an 18-gene gastric panel (EGDP18) that correlates with histologic severity and serum eotaxin-3 levels (44). Although some cases are associated with IgE-mediated allergy, many reflect non-IgE-driven immune activation, highlighting the heterogeneity of pathogenic pathways similar to EoE discussed earlier. Interestingly, molecular studies suggest that isolated eosinophilic colitis has a distinct transcriptomic profile, with marked upregulation of *CCL11* and *CLC*, and relatively little overlap with other EGIDs, indicating that it may be biologically distinct (45).

### Histologic diagnosis

Eosinophils are normal constituents of the lamina

propria throughout much of the GI tract, absent only in the esophagus. Their density varies by region, age, and environmental factors. In the stomach, normal counts in adults and children are generally under 10 eos/hpf in both antrum and body (46). In the normal small intestine, the medians are approximately 18–20 eos/hpf in the duodenum in pediatric population (47), with higher counts toward the ileum. The normal colon shows a proximal-to-distal gradient, with the right colon typically harboring the highest counts. In normal adult colon, the means in the most densely populated field are around 15–20 eos/hpf, though upper ranges may vary geographically (48).

Notably, there are still no widely accepted criteria for histologic diagnosis of EGE. Proposed diagnostic thresholds differ among studies. For eosinophilic gastritis, Turner *et al.* recommend  $\geq 30$  eos/hpf in at least 5 hpfs (49). For duodenal disease, the same threshold ( $\geq 30$  eos/hpf) in at least 3 hpfs is suggested. In the colon, Shoda *et al.* advocate segment-specific cutoffs: ascending colon  $\geq 100$  eos/hpf, descending colon  $\geq 85$  eos/hpf, sigmoid colon  $\geq 65$  eos/hpf (45), whereas Awad *et al.* favor a simpler threshold of  $\geq 30$  eos/hpf in the most densely populated field (48). More recently, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggested threshold peak eosinophil counts for the diagnosis of childhood non-EoE EGIDs as follows: stomach  $\geq 30$  eos/hpf, duodenum  $\geq 50$  eos/hpf, terminal ileum  $\geq 60$  eos/hpf, cecum and ascending colon  $\geq 100$  eos/hpf, transverse and descending colon  $\geq 80$  eos/hpf, and rectum and sigmoid colon  $\geq 60$  eos/hpf (50).

In addition to numerical counts, certain histologic features strengthen the diagnosis: confluent sheets of eosinophils in the lamina propria, eosinophilic cryptitis or crypt abscesses, subepithelial clustering, marked degranulation, and infiltration of the muscularis mucosae or submucosa if evaluable (51). In mucosal-predominant disease, an overall increase in the number of lamina propria eosinophils, usually more than double the normal site-specific value, is a particularly robust indicator for the diagnosis (Figure 2A-2C).

### Challenges in diagnosis

The histologic diagnosis of EGE is complicated by several factors. Because eosinophils are part of the normal mucosal immune repertoire, distinguishing physiologic

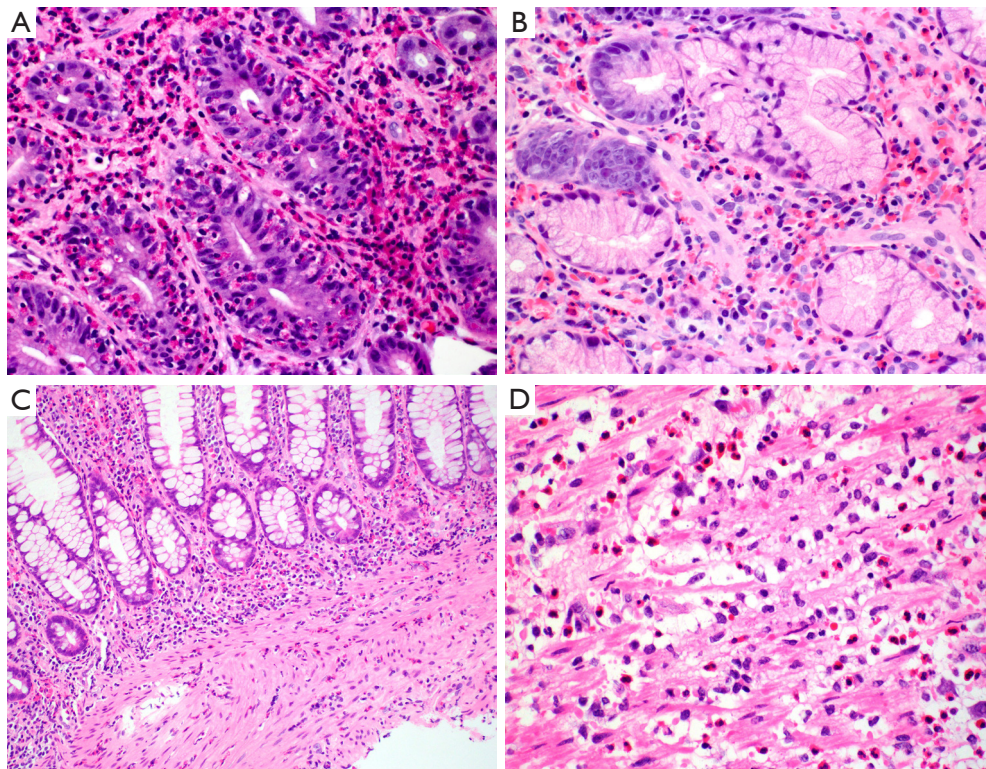


**Figure 2** Eosinophilic gastroenteritis. (A) Eosinophilic gastritis showing numerous eosinophils infiltrating the lamina propria. Eosinophilic cryptitis is also prominent in this case (hematoxylin-eosin stain, original magnification  $\times 400$ ). (B) Eosinophilic duodenitis (hematoxylin-eosin stain, original magnification  $\times 400$ ). (C) Eosinophilic colitis with prominent eosinophil infiltration of the muscularis mucosae (hematoxylin-eosin stain, original magnification  $\times 200$ ). (D) Mural form eosinophilic colitis showing eosinophil infiltration of the muscularis propria with damage of the muscle fibers (hematoxylin-eosin stain, original magnification  $\times 400$ ).

from pathologic levels requires reliable, site-specific reference ranges. In adults, there is still no consensus on histologic cutoffs, whereas pediatric guidelines are more prescriptive (50). The proposed histologic cutoffs are summarized in *Table 3*. The disease's patchy nature means that limited sampling may miss diagnostic foci; multiple biopsies from affected and apparently unaffected mucosa are advisable. Clinical, laboratory, and endoscopic findings rarely point definitively to EGE, as they overlap with many other GI disorders (34,38). Apparently, secondary causes can closely mimic idiopathic EGE, and peripheral eosinophilia is absent in a substantial subset. Furthermore, mucosal biopsies may appear normal when inflammation is confined to deeper layers, as in mural or serosal disease (*Figure 2D*) (52).

Since the diagnosis of EGE primarily relies on the overall increase in the number of lamina propria eosinophils, it can be a challenge for borderline cases that require a careful counting. Pathologists may use different

microscopes with different  $\times 40$  lenses to report eosinophil counts in hpf, and thus the results may not be reproducible among pathologists. There has been no standardized definition for hpf in terms of field area, but  $0.237 \text{ mm}^2$  has been suggested, which corresponds to a field diameter of 0.55 mm or an ocular lens with a field number of 22 mm (49). Apparently, cells with intact or partial nuclei should be counted. Discrete clusters of eosinophil granules without discernable nuclei should also be included. However, scattered, haphazardly distributed eosinophil granules should not be counted (49).

### **Differential diagnosis**

Primary EGE must be distinguished from secondary GI eosinophilia due to other causes. Infectious etiologies include helminths such as *Strongyloides* and *Anisakis*, as well as protozoal pathogens such as amebiasis. Inflammatory

**Table 3** Proposed diagnostic thresholds for eosinophilic gastrointestinal disease

| Site                            | Threshold (eosinophils/hpf) |
|---------------------------------|-----------------------------|
| Adults                          |                             |
| Esophagus                       | ≥15                         |
| Gastric antrum/body             | ≥30 in ≥5 hpfs (49)         |
| Duodenum                        | ≥30 in ≥3 hpfs (49)         |
| Jejunum/ileum                   | >50–56 (51)                 |
| Ascending colon                 | ≥100 (45)                   |
| Descending colon                | ≥85 (45)                    |
| Sigmoid colon                   | ≥65 (45)                    |
| Children                        |                             |
| Esophagus                       | ≥15                         |
| Stomach                         | ≥30 (50)                    |
| Duodenum                        | ≥50 (50)                    |
| Terminal ileum                  | ≥60 (50)                    |
| Cecum and ascending colon       | ≥100 (50)                   |
| Transverse and descending colon | ≥80 (50)                    |
| Sigmoid colon and rectum        | ≥60 (50)                    |

hpf, high power field.

bowel disease, celiac disease and collagenous gastritis are other important considerations, which can show prominent eosinophils in lamina propria infiltrates (Figure 3A–3C). Medications such as nonsteroidal anti-inflammatory drugs, rifampicin, and clozapine can trigger marked tissue eosinophilia. Systemic disorders, including hypereosinophilic syndrome, connective tissue diseases, vasculitis, mastocytosis (discussed below), and Langerhans cell histiocytosis (Figure 3D), must also be excluded (41,53). Certain neoplasms and polypoid lesions (such as inflammatory polyp and inflammatory fibroid polyp) can provoke prominent eosinophilic inflammation. Careful histologic analysis and integration of histologic findings with clinical and endoscopic data are essential to accurate diagnosis.

Current controversies

Several issues remain unsettled. For terminology, international consensus now favors site-specific terms, including eosinophilic gastritis, enteritis, and colitis, over

the broader term “eosinophilic gastroenteritis”, except when both stomach and small bowel are involved (54). Histologic thresholds are another area of debate, with ongoing discussion over whether universal or site- and population-specific cutoffs are preferable. Molecular diagnostics hold promise for refining diagnosis and classification but are not yet part of routine practice. The extent to which EGE overlaps with other inflammatory GI disorders such as inflammatory bowel disease and collagenous gastritis, or stands as a distinct disease, remains to be clarified (55).

Mastocytic GI diseases

Introduction

Mast cells are distributed throughout the GI tract, where they participate in host defense, allergic responses, and modulation of mucosal immunity (56). They are scattered within the lamina propria, concentrated around blood vessels, nerves, and beneath the epithelial layer, with density varying by anatomic site and individual factors. In pathologic conditions, mast cell numbers and behavior may be altered.

Two broad categories of mast cell related GI pathology are recognized. The first is mastocytosis, a clonal mast cell proliferation most often associated with *KIT* mutations, immunophenotypic aberrancies, and sometimes systemic involvement. It manifests as abnormal mucosal mast cell aggregates, often with a spindled morphology. The second category is so-called “mastocytic enterocolitis”, an entity proposed for patients with irritable bowel syndrome (IBS). The number of lamina propria mast cells is supposed to be increased in the absence of aggregates, cytologic atypia, or immunophenotypic aberrations. The latter remains controversial, with uncertainty regarding its pathogenesis, clinical significance, and even existence as a discrete disease entity.

To pathologists, these conditions present distinct diagnostic challenges. Mast cell-rich infiltrates in mucosal biopsies are often subtle, can mimic or overlap with other inflammatory processes, and require careful morphologic, immunohistochemical, and sometimes molecular evaluation. Misinterpretation may lead to over-investigation or, conversely, to missed diagnoses, particularly when systemic disease is present without cutaneous manifestations (57).

Mastocytosis involving the GI tract

Mastocytosis is a clonal proliferation of mast cells that can

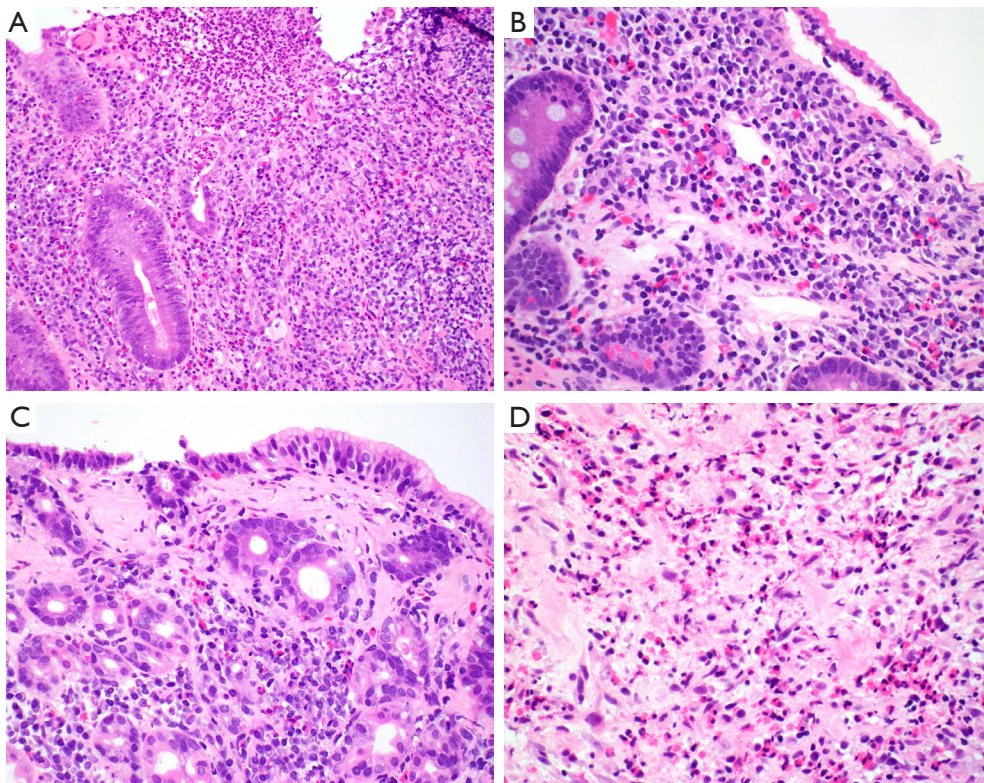


**Figure 3** Examples of gastrointestinal disorders with eosinophilia. (A) Ulcerative colitis (hematoxylin-eosin stain, original magnification  $\times 200$ ). (B) Celiac disease (hematoxylin-eosin stain, original magnification  $\times 400$ ). (C) Collagenous gastritis (hematoxylin-eosin stain, original magnification  $\times 400$ ). (D) Langerhans cell histiocytosis presenting as a polypoid lesion. Note the presence of spindle cells (hematoxylin-eosin stain, original magnification  $\times 400$ ).

involve one or multiple organs. According to the World Health Organization (WHO), it is classified into three main forms: cutaneous mastocytosis, confined to the skin and most often seen in children where it tends to be self-limited; systemic mastocytosis (SM), defined by extracutaneous involvement, most frequently in the bone marrow, liver, spleen, lymph nodes, and GI tract; and mast cell sarcoma, an aggressive and exceedingly rare neoplasm. SM is further subtyped into indolent, smoldering, and aggressive disease, as well as SM with an associated hematologic neoplasm and mast cell leukemia (58). Indolent SM is the most common form and is compatible with long-term survival, whereas aggressive variants carry a poorer prognosis.

The diagnostic framework for SM normally requires either one major criterion plus at least one minor criterion, or at least three minor criteria (59). The major criterion is the presence of multifocal, dense infiltrates of at least 15 mast cells in aggregates in the bone marrow or other extracutaneous organs, including the GI mucosa. Minor

criteria include (I) atypical cytology, with at least 25% of mast cells showing spindle-shaped or otherwise abnormal morphology; (II) D816V or another activating *KIT* point mutation in an extracutaneous site; (III) aberrant co-expression of CD2 and/or CD25 alongside typical mast cell markers such as CD117 and tryptase; and (IV) a persistently elevated serum tryptase level exceeding 20 ng/mL, unless attributable to an associated hematologic neoplasm.

#### *Histologic features in GI biopsies*

GI involvement by SM is common, which was reported in 14–85% of cases. GI involvement can be the presenting manifestation, particularly in indolent forms (60). Most cases are asymptomatic, although some may have nonspecific GI symptoms. Histologically, mast cell aggregates are most often found in the lamina propria but may extend into submucosa. They can be compact clusters or sheets of mast cells, sometimes subepithelial or perivascular, often with a

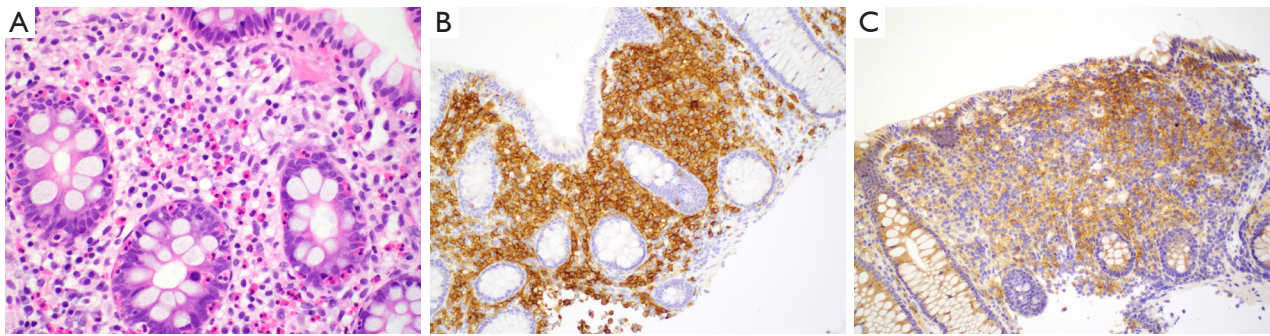


**Figure 4** Mastocytosis involving the colon. (A) Histology showing lamina propria aggregates of mast cells, some having a spindled morphology. Note the presence of prominent eosinophils (hematoxylin-eosin stain, original magnification  $\times 400$ ). (B) Immunostaining for CD117 highlighting sheets of mast cells in the lamina propria (original magnification  $\times 200$ ). (C) Mast cells co-expressing CD25 (immunohistochemistry, original magnification  $\times 200$ ).

spindled morphology (Figure 4A). Infiltrates may be subtle and easily overlooked or mistaken for histiocytes, lymphoid aggregates, or other inflammatory foci (61).

Routine H&E often underestimates mast cells; immunohistochemistry for CD117 (KIT) and tryptase improves detection (Figure 4B). Aberrant CD25 and/or CD2 expression strongly supports a clonal process (Figure 4C), though the staining patterns of these markers can be patchy. Demonstration of *KIT* D816V mutation confirms clonality when present, but absence does not exclude the diagnosis.

#### ***Differential diagnosis of mucosal mast cell aggregates***

Increased mast cells in mucosal biopsies may also occur in reactive conditions, including allergic gastroenteritis, parasitic infections, inflammatory bowel disease, and other chronic inflammatory processes. The distinction between reactive mast cell hyperplasia and clonal mastocytosis rests on aggregation pattern, cytologic atypia, aberrant immunophenotype, and molecular findings. Aggregates of  $\geq 15$  mast cells with spindled morphology and CD25/CD2 co-expression are highly suggestive of mastocytosis. In the absence of aggregates or atypia, increased mast cells should not be over-interpreted without supportive clinical or molecular data (62).

#### ***Incidental mast cell aggregates***

Small mast cell aggregates may be encountered incidentally in otherwise normal GI biopsies. Studies have shown that such incidental findings, in asymptomatic patients without systemic features, often represent benign reactive changes

and do not reflect or progress to generalized disease (63). In such cases, extensive systemic workup, such as bone marrow biopsy and/or *KIT* mutation analysis, may not be warranted.

#### ***Proposed diagnostic criteria for mastocytic enterocolitis (ME)***

ME was proposed in 2006 for a subset of patients with intractable chronic diarrhea. By definition, these patients have normal endoscopy and normal histology (Figure 5A), but an increased number of lamina propria mast cells in mucosal biopsies as defined by  $>20$  mast cells/hpf by mast cell immunohistochemistry (Figure 5B) (64). Unlike mastocytosis, ME lacks mast cell aggregates, spindled morphology or cytologic atypia, CD25/CD2 co-expression, and *KIT* mutations. Interestingly, some studies report that patients meeting ME criteria respond to mast cell-directed therapies such as antihistamines or mast cell stabilizers (64,65). However, these studies are uncontrolled and require further validation.

#### ***Controversies and limitations***

The concept of ME remains debated. Several studies have failed to demonstrate a clear-cut threshold from healthy controls (Table 4). In fact, mast cell density overlaps substantially between patients with functional diarrhea, IBS, inflammatory bowel disease in remission, and healthy individuals (72). Moreover, mast cell counts may vary with biopsy sites, technical factors, and staining methods. In fact, a meta-analysis that analyzed nine studies reporting an increased number of mast cells in the bowel mucosa of patients with chronic diarrhea concluded that no consensus

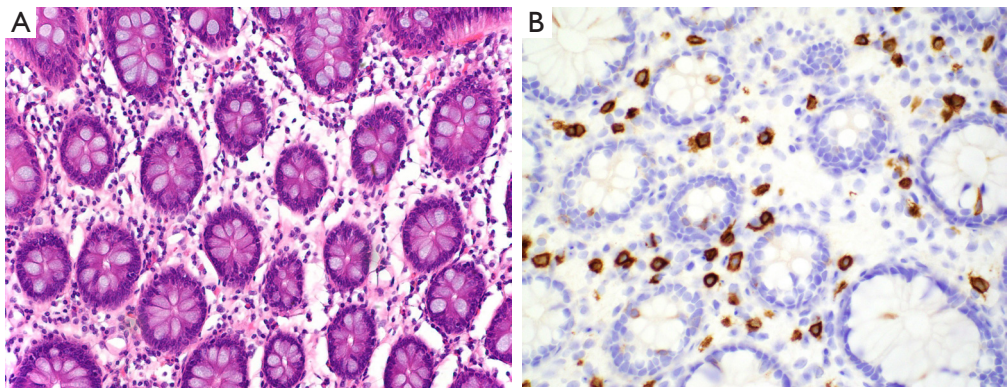


**Figure 5** So-called “mastocytic enterocolitis”. (A) A colonic biopsy showing normal histology (hematoxylin-eosin stain, original magnification  $\times 200$ ). (B) Immunostaining for CD117 highlighting intramucosal mast cells (original magnification  $\times 400$ ).

**Table 4** Mast cell counts in GI tract in asymptomatic controls and IBS-diarrhea patients

| Study                           | Asymptomatic control (per hpf), mean $\pm$ SD/mean (range)/mean $\pm$ SD (range)             | IBS-diarrhea (per hpf), mean $\pm$ SD/mean (range)/mean $\pm$ SD (range) |
|---------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Jakate <i>et al.</i> (64)       | Duodenum: $13.2 \pm 3.7$<br>Colon: $13.6 \pm 3.1$                                            | $25.7 \pm 4.5$                                                           |
| Park <i>et al.</i> (66)         | Terminal ileum: $37.9 \pm 5.8$<br>Ascending colon: $37.4 \pm 6.2$<br>Rectum: $37.3 \pm 6.0$  | $49.1 \pm 7.4$<br>$47.7 \pm 7.1$<br>$47.8 \pm 7.6$                       |
| Hahn and Hornick (67)           | Stomach: 12 (5–21)<br>Duodenum: 27 (4–51)<br>Terminal ileum: 32 (21–40)<br>Colon: 21 (10–31) | 20 (12–31)                                                               |
| Zare-Mirzaie <i>et al.</i> (68) | Colon: $14.2 \pm 3.4$                                                                        | $21.3 \pm 4.8$                                                           |
| Doyle <i>et al.</i> (69)        | Colon: 26 (11–55)                                                                            | 30 (13–59)                                                               |
| Sethi <i>et al.</i> (70)        | Colon: $21.1 \pm 8.7$ (8–47)                                                                 | $30.7 \pm 10.5$ (13–67)                                                  |
| Fan <i>et al.</i> (71)          | Colon: $16.6 \pm 4.0$ (9–22)                                                                 | $19.5 \pm 6.5$ (9–31)                                                    |
| Reed <i>et al.</i> (43)         | Stomach: $18.1 \pm 7.2$<br>Duodenum: $23.6 \pm 8.1$                                          | ND                                                                       |

GI, gastrointestinal; hpf, high power field; IBS, irritable bowel syndrome; ND, not done; SD, standard deviation.

could be found on the cutoff point. The overlap in range between patients and controls was too great to be of clinical significance. Therefore, a routine evaluation of mast cell count in normal GI biopsies is not justified (73).

**Mast cell activation syndrome (MCAS)**

MCAS is a disorder characterized by inappropriate mast

cell activation leading to dysregulated mast cell mediator release. It can be classified as primary (associated with clonal mast cell disorders), secondary (triggered by conditions such as allergy, autoimmune disease, or infection), or idiopathic (no trigger or clonality) (74–76). GI symptoms are common, including abdominal pain, diarrhea, nausea, and bloating (3).

MCAS cannot be diagnosed by mast cell counts in tissue, because it is biochemical mediator-driven rather than

mast cell proliferation. Tissue studies are mainly useful to exclude clonal mast cell disorders such as SM. GI biopsies from patients with MCAS are often histologically normal or shows only a subtle increase in mast cell count, without aggregates or atypia. The diagnosis is clinical, based on episodic symptoms, evidence of mast cell mediator release (elevated serum tryptase or urinary histamine metabolites during flares), and response to anti-mast cell therapy. Immunostaining for mast cells in GI biopsies has no diagnostic value for MACS.

### ***Practical approach for pathologists***

When evaluating for potential mast cell disorders in GI biopsies, it is important to assess for aggregates and cytologic atypia (mainly the spindled morphology). If aggregates are present, immunostaining for CD25 and/or CD2 should be performed. Molecular testing for *KIT* mutation may be considered but is not absolutely necessary. In such cases, communication with the clinician regarding possible SM and the need for further workup (including bone marrow biopsy) is warranted.

Outside the setting of mast cell aggregates, immunostains for mast cells on GI biopsies for the diagnosis of ME or MCAS should be discouraged (72,77). It is absolutely unnecessary to perform additional CD25 and/or CD2 immunostains or *KIT* mutation analysis. Nevertheless, pathologists may still receive requests from gastroenterologists or rheumatologists for mast cell counting. When the request cannot be refused, many pathologists choose to just report mast cell counts without further commenting whether the counts are increased or within normal range.

### **Conclusions**

Eosinophilic and mastocytic GI diseases represent a diverse and evolving spectrum of disorders in which immunologically mediated inflammation plays a central role. Recent advances in epidemiologic surveillance, histologic scoring systems, and molecular characterization have refined our understanding of their pathogenesis and diagnostic criteria. Nonetheless, significant challenges persist, particularly in differentiating primary from secondary forms, defining universally applicable histologic thresholds, and establishing the clinical significance of certain histologic patterns.

EGID is characterized by eosinophilic infiltration of one or more segments of the GI tract. It is traditionally divided into mucosal, mural and serosal forms with diverse

clinicopathologic characteristics. Histologic diagnosis of mucosal form is site-dependent and based on the overall increase in the number of lamina propria eosinophils. This can be a challenge for borderline cases, which may require a high index of suspicion and careful counting of intramucosal eosinophils.

There are three potential types of mast cell involvement of the GI tract: abnormal mucosal mast cell aggregates (mastocytosis), so-called ME, and MCAS. Mastocytosis typically shows a spindled morphology and co-expression of CD25 and/or CD2, and may show *KIT* mutation. An incidental finding of mast cell aggregates in GI biopsies may or may not represent SM, but majority of patients have an indolent disease and thus further work-up with bone marrow biopsy may not be necessary. On the other hand, ME remains a controversial entity. At present, there are no established normal reference ranges, nor are there accepted thresholds for the diagnosis based on mast cell count. In addition, there is no compelling evidence that mast cell counts are of clinical utility in the evaluation and management of IBS and MCAS patients. Therefore, use of immunostains to quantify mast cells in normal-appearing GI mucosa is not justified in the workup of patients with suspected IBS or MCAS.

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