Eosinophilic Gastrointestinal Diseases Beyond Eosinophilic Esophagitis

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The eosinophilic gastrointestinal diseases (EGIDs) are chronic, immune-mediated conditions characterized clinically by GI symptoms and histologically by pathologic infiltration of the GI tract by eosinophils. The most well-studied is eosinophilic esophagitis (EoE), but non-EoE EGIDs are becoming more frequently encountered. These have traditionally been classified by the predominant location inflammation, including eosinophilic gastritis (EoG; stomach only), eosinophilic enteritis (EoN; small bowel only), and eosinophilic colitis (EoC; colon only) (1,2). However, multiple locations can be involved (e.g., gastric and small bowel involvement), specific segments of the small bowel can be named (e.g., eosinophilic duodenitis [EoD]), and efforts are underway to standardize this nomenclature. The non-EoE EGIDs are considered rare diseases, with studies of administrative databases estimating the prevalence to be approximately 3–8/100,000 or ~50,000 cases in the United States (3). However, recent data suggest these conditions may be underdiagnosed (4). In this article, I will review my approach to the diagnosis and management of the non-EoE EGIDs, highlighting a number of principles that can be applied in most settings.

THE DIAGNOSTIC ROADMAP

Diagnosis of the non-EoE EGIDs can be challenging. In contrast to the esophagus where eosinophils are normally not present, eosinophils are constituent elements in the mucosa of other parts of the GI tract, the clinical presentation is nonspecific, and diagnostic delay is common (5). However, even without published diagnostic guidelines (although these are forthcoming), there is a deliberate approach that I follow to ensure an accurate and timely clinicopathologic diagnosis (Figure 1).

Suspecting nonspecific symptoms

Symptoms of the non-EoE EGIDs tend to reflect the area of the GI tract that is predominantly effected (6). For EoG, symptoms include abdominal pain, cramping or bloating, nausea, vomiting, poor appetite, early satiety, or weight loss. When the small bowel is involved symptoms are similar, although diarrhea and malabsorption symptoms can been seen. In EoC, abdominal pain and diarrhea are common, and lower GI bleeding can be noted. The difficulty is that these symptoms are nonspecific, and more common conditions will be suspected before EGIDs. An elevated peripheral eosinophil count or low serum albumin can be helpful (7), but these are not present in all patients. Similarly, although EGIDs are believed to be allergic conditions, not all patients have atopy (6). Fatigue or pallor can be seen if there is accompanying iron deficiency anemia, peripheral edema can be seen with hypoalbuminemia from protein-losing enteropathy (sometimes out of proportion to GI symptoms), and ascites can be seen with serosal involvement. I think of EGIDs as a diagnostic possibility when patients continue to have these ongoing symptoms or signs without another recognized cause.

Engaging in endoscopy

Persistent upper GI symptoms will trigger an upper endoscopy, but the endoscopic findings in the non-EoE EGIDs may be nonspecific or the appearance may be normal (6,8), so a careful examination and high level of suspicion are required (Figure 2). When present, endoscopic findings in the stomach can include erythema, congestion, granularity, erosion, ulceration, friability, nodularity, and pyloric stenosis; an endoscopic grading system for these findings is being developed (9). In the duodenum and small bowel, findings include erythema, congestion, villous dropout or flattening, salmon-colored lesions, erosions, ulceration, and stenosis. Stenoses can be a clue that the muscle layer of the GI tract rather than the mucosa may be involved. Even with accompanying lower GI symptoms, colonoscopy not need be performed in every case of suspected or known EGID, but findings can include erythema, congestion, and ulceration.

Broadly biopsying

Regardless of the endoscopic appearance, biopsies are needed to evaluate for eosinophils and other architectural changes. In EoE, esophageal eosinophilic inflammation is patchy, and multiple esophageal biopsies from different locations are required to ensure diagnosis. Emerging data suggest EoG and EoD are analogous, with 1 analysis suggesting that 8 gastric (4 antral; 4 body) and 4 duodenal biopsies may be the optimal number to detect relevant eosinophilia (10). The corollary is that if only 2–4 biopsies are taken, the diagnosis may be missed. These data have altered my approach, and when I have a suspicion for EoG or EoD, I will obtain this more extensive number of biopsies, although it is not known whether obtaining biopsies more distally in the duodenum or proximal jejunum further increases the yield. A complicating factor is that mucosal biopsies may seem normal with either muscle layer or serosal involvement, but full-thickness GI tract biopsies are reserved for special circumstances.

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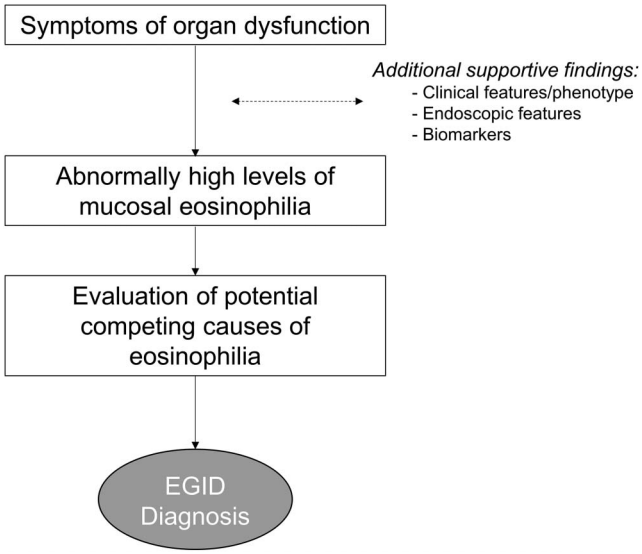

Figure 1. Clinicopathologic diagnostic approach to non-EoE EGIDs. Chronic symptoms, although nonspecific, are often related to the area of the GI tract that is predominantly involved. Other clinical features such as atopy, peripheral eosinophilia, or hypoalbuminemia, and endoscopic abnormalities, can be supportive but are not present in a sizable proportion of patients, so a high degree of suspicion is needed to consider the diagnosis clinically. Biomarkers are not yet widely available. When performing endoscopy, a biopsy protocol that samples multiple areas of the stomach and duodenum is required, and an increasing number of biopsies will maximize diagnostic sensitivity. Pathologically elevated eosinophil levels are required, but the diagnosis cannot be confirmed until an evaluation of potential causes of GI tract eosinophilia has been performed and other causes excluded. EGID, eosinophilic gastrointestinal disease; EoE, eosinophilic esophagitis; GI, gastrointestinal.

Highlighting histology

Obtaining biopsies is only part of the story. First, because EGIDs are not commonly encountered, I feel it is important to communicate closely with my colleagues in pathology. This allows them to know a non-EoE EGID is suspected and prompts them to directly assess for eosinophilic inflammation, quantify the eosinophil count, and examine associated histologic features (e.g., epithelial involvement; microabscesses; and signs of chronicity) (11). Then, the major question is whether there are a pathologically elevated number of eosinophils. There is a gradient of normal levels of eosinophils in the GI tract. In the stomach, normal values are in the 5–10 eosinophils per high-power field (eos/hpf) range, increase to 10–25 in the duodenum, and can be as high as 50 or more in the terminal ileum and cecum (11). Although definitive diagnostic thresholds are still forthcoming, a consensus is developing, particularly for clinical trials, for requiring ≥30 eos/hpf in at least 5 hpfs in the stomach (to show a more diffuse involvement) for EoG, and either ≥30 eos/hpf in at least 3 hpfs or ≥50 eos in at least 1 hpf in the duodenum or small bowel to diagnosis EoD, or EoN, with higher thresholds in the colon. A recent study examined diagnosis specificity for different thresholds and suggested that the higher the eosinophil count cutpoint, the fewer hpfs required (12). Assessing for mast cells is not yet standard. In practice, I typically look for ≥30 eos in at least 1 hpf in the stomach and ≥30–50 eos in the small bowel, but with evidence that it is not simply a focal finding.

Definitive diagnosis: defeating the differential

Having suggestive GI symptoms and pathologically elevated eosinophils is not enough to diagnose a non-EoE EGID. It is critical to evaluate for other potential causes of increased GI eosinophils and conditions that have been associated with eosinophilia (Table 1). Although some of these conditions can be excluded with a thorough history and physical, others require a more extensive evaluation. I will typically perform routine chemistries, albumin, complete blood count with differential (to assess for peripheral eosinophilia), and iron studies and ferritin (if anemia is present). If blood eosinophils are elevated, I will check stool studies and serology for parasites; if there is concern for hypereosinophilic syndrome (peripheral eos $\geq 1.5 \times 10^9$/L), I will refer to hematology. Additional testing is dependent on presentation and can include cross-sectional imaging or enterography, nutritional evaluation, ascitic fluid analysis, colonoscopy, or capsule enteroscopy. Once I am convinced that there is not another cause of eosinophilia, I will definitively diagnose a non-EoE EGID.

MULLING MANAGEMENT OPTIONS

I find management of non-EoE EGIDs to be more complicated than diagnosis because there are no US FDA-approved medications, only 1 randomized trial of an experimental pharmacologic agent (13), and only 1 prospective dietary elimination study (14). Therefore, most experience is based on case series and retrospective cohort studies, there is substantial treatment variability between centers (6), and because multiple areas of the GI tract can be involved and patients can have complications of their disease, overlapping approaches may be needed.

For pharmacologic options, proton pump inhibitors can be used if there are gastric erosions or ulcers present but lack efficacy data in non-EoE EGIDs. There have been reports that leukotriene antagonists (montelukast), mast cell stabilizers (cromolyn; ketotifen), or immunomodulators (6-mercaptopurine; azathioprine; and methotrexate) can be used, but data are limited (1,2). Corticosteroids are a

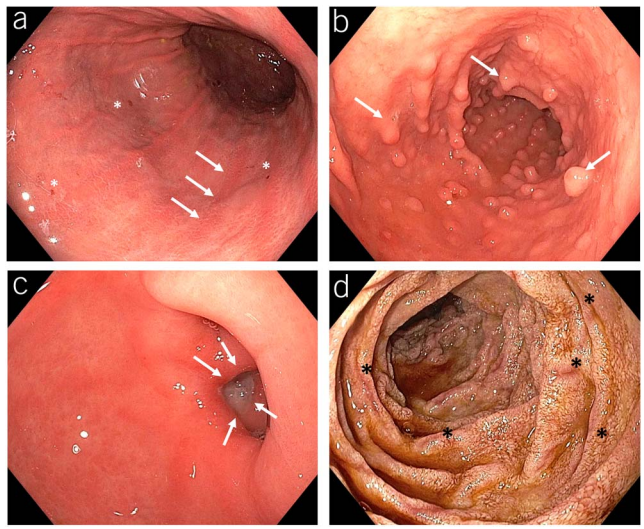

Figure 2. Endoscopic findings in eosinophilic gastritis and duodenitis. (**a**) Gastric body with erythema (white arrows), congestion, granularity, and a few small erosions (white asterisks). (**b**) Gastric body and antrum with nodularity (white arrows), congestion, and erythema. (**c**) Pyloric channel ulcer (white arrows). (**d**) Duodenal view with villous dropout (black asterisks), erythema, and congestion.

Table 1. Differential diagnosis of gastrointestinal tract eosinophilia

Infections (parasites/helminths; *Helicobacter pylori*)
Hypereosinophilic syndrome
Drug hypersensitivity reactions
Inflammatory bowel disease
Celiac disease
Malignancy
Adrenal insufficiency
Graft vs host disease
Connective tissue/autoimmune disorders (vasculitis; eosinophilic granulomatosis with polyangiitis)
Toxic or food exposures (transient)

mainstay of treatment. Systemic agents are effective but limited to short-time use, and patients often flare when the dose is weaned and require subsequent retreatment. Topical steroids directed to different areas of the GI tract are appealing, but existing budesonide enteral release products must be modified. The pills can be opened and crushed to target the stomach, opened with the granules swallowed for the proximal small bowel, and swallowed intact for the distal small bowel and colon (15). The difficulty is that with the large surface area to be covered, and with dosing not well established, broad steroid dosing recommendations are not currently available, and doses should be individualized.

Similar to EoE, empiric dietary elimination has been reported to be successful for patients with non-EoE EGID (2), but my experience is that this is not as effective as what is seen in EoE. However, elemental formula is an option for severe patients, and a recent prospective cohort study of 15 patients with EoG/EoN showed an 100% response rate (<30 eos/hpf) after 6 weeks of treatment (14). Not only does this confirm that this treatment is effective but also strongly suggests that food antigens drive EoG/EoN pathogenesis.

Given the profound need for treatment options and the increasing knowledge of EGID pathogenesis, there are a number of biologic agents under study for non-EoE EGIDs, but none are yet approved for these conditions. A phase 2 study of lirentelimab, which targets the Siglec-8 receptor and depletes eosinophils and inhibits mast cells, showed a marked reduction in gastric and duodenal eosinophil levels and improved symptoms, as compared to placebo (13). Other candidate biologics being investigated include benralizumab (anti-interleukin [IL]-5r antibody that depletes eosinophils) and dupilumab (anti-IL-4r antibody approved for asthma and atopic dermatitis); there have also been case reports of mepolizumab (anti-IL-5 antibody) and vedolizumab (anti-integrin antibody) being used for the non-EoE EGIDs.

Given these options and the lack of available treatments, I feel that clinical trials may be the best option for many patients with non-EoE EGID if they meet inclusion criteria or can potentially receive a placebo. Outside of trials, I reserve systemic steroids and elemental formula for the most severe patients. My general approach is to select a treatment using a shared decision-making approach with the patient. I then perform a follow-up endoscopy (for EoG/EoD/EoN) after approximately 3 months of treatment, so I can follow not only symptoms but also endoscopic and histologic response as well.

FUTURE DIRECTIONS

Diagnosis and management of the non-EoE EGIDs can be challenging. However, the field is rapidly evolving and developing fundamental data; similar to how EoE was 10–15 years ago, the non-EoE EGID field is set to greatly expand. There are questions about details of diagnosis, options for treatments, logistics for monitoring, and long-term outcomes. Despite this, I believe a careful diagnostic approach, having a high suspicion for a non-EoE EGID, taking an adequate number of biopsies, collaborating with pathologists, and working the differential will lead to the correct diagnosis. Although many patients can be treated with a combination of topical steroids, proton pump inhibitors, or diet elimination, I hope we will soon be addressing the question of where novel pharmaceutical agents will fit into our treatment algorithm. These advances will benefit patients with non-EoE EGIDs and streamline diagnostic and therapeutic approaches going forward.

CONFLICTS OF INTEREST

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