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Gastrointestinal Manifestations of Hypereosinophilic Syndromes and Mast Cell Disorders: a Comprehensive Review

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Abstract
Hypereosinophilic syndrome and mastocytosis are relatively rare proliferative diseases encountered in the general population. However, allergists frequently consider these disorders in the differential of patients presenting with gastrointestinal, pulmonary, cutaneous, and allergic symptoms. Gastrointestinal symptoms are some of the most frequent and/or debilitating aspects of both disease states and in many cases lead to poor quality of life and functional limitation for the patient. They are the third most common clinical manifestation in hypereosinophilic syndrome and have been found to be the most distressful aspect of the disorder in those with systemic mastocytosis. Both eosinophils and mast cells play integral parts in normal gut physiology, but when and how exactly their effector functionality translates into clinically significant disease remains unclear, and the available literature regarding their pathophysiology remains sparse. Eosinophils and mast cells even, in fact, may not necessarily function in isolation from each other but can participate in bidirectional crosstalk. Both are affected by similar mediators and can also influence one another in a paracrine fashion. Their interactions include both production of soluble mediators for specific eosinophil and mast cell receptors (for example, eosinophil recruitment and activation by mast cells releasing histamine and eotaxin) as well as direct physical contact. The mechanistic relationship between clonal forms of hypereosinophilia and systemic mastocytosis has also been explored. The nature of gastrointestinal symptomatology in the setting of both hypereosinophilic syndrome and mast cell disease is frequently manifold, heterogeneous, and the lack of better targeted therapy makes diagnosis and management challenging, especially when faced with a substantial differential. Currently, the management of these gastrointestinal symptoms relies on the treatment of the overall disease process. In hypereosinophilia patients, systemic corticosteroids are mainstay, although steroid-sparing agents such as hydroxyurea, IFN-α, methotrexate, cyclosporine, imatinib, and mepolizumab have been utilized with varying success. In mastocytosis patients, anti-mediator therapy with antihistamines and mast cell stabilization with cromolyn sodium can be considered treatments of choice, followed by other therapies yet to be thoroughly studied, including the role of the low-histamine diet, corticosteroids, and treatment of associated IBS symptoms. Given that both eosinophils and mast cells may have joint pathophysiologic roles, they have the potential to be a combined target for therapeutic intervention in disease states exhibiting eosinophil or mast cell involvement.

Keywords Gastrointestinal · Hypereosinophilic syndrome · Systemic mastocytosis · Mast cell · Eosinophil · Eosinophilic gastrointestinal diseases

Abbreviations

HES	Hypereosinophilic syndromes
AEC	Absolute eosinophilic count
HEUS	Hypereosinophilia of unknown significance
EGPA	Eosinophilic granulomatosis with polyangiitis
EGIDs	Eosinophilic gastrointestinal diseases
M-HES	Hypereosinophilic syndrome (myeloid variant)
L-HES	Hypereosinophilic syndrome (lymphocytic variant)
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IL	Interleukin
ILCs	Innate lymphoid cells
TNF	Tumor necrosis factor

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CCL	Chemokine ligand
CCR	Chemokine receptor
FcεRI	High-affinity immunoglobulin E (IgE) receptor
IFN	Interferon
VEGF	Vascular endothelial growth factor
MPS	Myeloproliferative syndrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
ALPS	Autoimmune lymphoproliferative syndrome
SLE	Systemic lupus erythematosus
IBD	Inflammatory bowel disease
HPF	High-power field
FDA	Food and Drug Administration
EoE	Eosinophilic esophagitis
IBS	Irritable bowel syndrome
SCF	Stem cell factor
MAdCAM-1	Mucosal vascular addressin cell adhesion molecule 1
VCAM-1	Vascular cell adhesion molecule 1
FOXO3	Forkhead box O3
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
CRH	Corticotropin releasing hormone
PAF	Platelet activating factor
PDG	Prostaglandin
LT(C,D,E)4	Leukotriene(C,D,E)4
ASM	Aggressive systemic mastocytosis
DSCG	Disodium cromoglycate
MMAS	Monoclonal mast cell activation syndrome
MCAS	Mast cell activation syndrome
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
eos	Eosinophils
MCs	Mast cells
AEU	Allergic effector unit

Introduction

Eosinophils and mast cells can play significant roles in gastrointestinal pathology and are associated with serious manifestations of disease in some instances. In this review, the pathophysiology, manifestations, diagnostic approaches, and management of gastrointestinal aspects of eosinophilia and mast cell disease are discussed, with a focus on hypereosinophilic syndromes and systemic mastocytosis in which gastrointestinal symptoms are among the most troublesome and frequent for patients. Diagnosis and management of these disorders requires familiarity with both primary and secondary etiologies since their gastrointestinal symptomatology can be various and non-specific, and treatment ultimately falls to management of the underlying problem. In addition to symptomatic treatment, both scenarios require surveillance for more serious complications, such as end-organ fibrosis and dysfunction in hypereosinophilia and the development of more aggressive disease in mastocytosis. It appears important to keep in mind, however, that significant variation between laboratory aberrancy and clinically significant manifestations of disease may exist; for example, in the setting of benign eosinophilia and familial hypertryptasemia as is later discussed. While both eosinophils and mast cells play normal, physiologic roles in the healthy gut, understanding their potential to cause problems remains an area rich for investigation. Studies investigating a possible role for mast cell activity in eosinophilic disease states and vice versa also remain in their infancy, suggesting that these cells do not act as separate entities and instead have a shared role in the pathogenesis of these and potentially other immunopathologic disorders.

Hypereosinophilic Syndromes

Hypereosinophilic syndromes (HES) are a constellation of heterogeneous disorders defined by persistent peripheral eosinophilia (absolute eosinophil count (AEC) > 1500/mm^3) with end-organ dysfunction in the absence of other etiologies. These syndromes are generally considered to encompass entities for which secondary, reactive causes (such as allergic disease or parasitosis) have been ruled out. Idiopathic HES, more specifically, is itself a diagnosis of exclusion, necessitating rule out of all primary causes of eosinophilia. The phrase "idiopathic hypereosinophilia" has been suggested as the preferred terminology to replace HES in situations where there is no end-organ damage [1]. The terms "benign eosinophilia" and "hypereosinophilia of unknown significance" (HEUS) have also been utilized in cases where hypereosinophilia occurs in the absence of clinical signs and symptoms [2]. HES have been otherwise classified into subtypes based on the etiology of eosinophilopoiesis (see "Pathophysiology" below).

In theory, all organs are susceptible to damage by infiltrating eosinophils including the gastrointestinal (GI) tract. GI involvement has been well-established and is the third most commonly reported clinical manifestation in patients with hypereosinophilia (up to 38%) [1], although clinical complications occur more frequently in other organ systems [3]. Hypereosinophilia presenting with gastrointestinal disease can manifest in many ways, including but not limited to eosinophilic gastritis, gastroenteritis, enteritis, colitis, chronic active hepatitis, hepatic lesions, cholangitis, eosinophilic

granulomatosis with polyangiitis (EGPA), hepatic vein thrombosis (Budd-Chiari Syndrome), and more (see "Clinical Manifestations and Presentation" below). These entities can be difficult to distinguish between other organ-restricted eosinophilic disorders such as those falling under the category of eosinophilic gastrointestinal disorders (EGIDs) as the distinction between them, if existent, is blurred. We focus on eosinophilic infiltration of the gut in association with peripheral hypereosinophilia in the first half of this review.

Pathophysiology

HES are disorders characterized by sustained eosinophilopoiesis. Such eosinophilopoiesis can result from either primary (clonal) or secondary mechanisms. "Primary" hypereosinophilic syndromes, also referred to as neoplastic HES by most, occur as a result of stem cell mutation. Acute and chronic eosinophilic leukemia are two examples of primary isolated eosinophilia that are historically distinguished from HES due to the presence of immature eosinophils. Primary hypereosinophilia can also be associated with other myeloid neoplasms; this subtype is also known as the myeloid variant HES or hypereosinophilic syndrome (myeloid variant) (M-HES) (see "Diagnostic Approach" below [4]). Patients with the FIP1L1-PDGFRA fusion are considered M-HES variant due to this pathologic mutation even if they do not necessarily meet all four (or more) historical, serologic, and/or pathologic criteria [5]. Reactive expansion of eosinophils may result from IL-5 overproduction, as in the case of IL-5 producing T cell subsets, also known as lymphocytic variant HES or hypereosinophilic syndrome (lymphocytic variant) (L-HES). As HES are diagnoses of exclusion, secondary eosinophil expansion by other mechanisms such as drug hypersensitivity reactions or other associated disease states (such as EGPA) require rule out as well. In 70–80% of patients with hypereosinophilia, however, no specific mechanism is found despite in-depth workup [6]. General concepts of eosinophilopoiesis leading to tissue injury in the gastrointestinal tract are illustrated schematically in Fig. 1.

Eosinophils are granulocytes derived from CD34+ pluripotent myeloid precursors in response to major eosinophil growth factor cytokines granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3 (interleukin-3), and most critically IL-5. Studies using gene knockout mice deficient in IL-5 found that peripheral or tissue eosinophilia do not develop despite baseline eosinophil production by the bone marrow, suggesting that regulation of eosinophil homeostasis more likely occurs at the level of gene transcription independently of cytokine expression. This process has been found regulated by GATA-1, GATA-2, and c/EBP transcription factors and takes about 8 days to occur. Sources of IL-5 include Th2 cells and type 2 innate lymphoid cells (ILC2s). Once matured, eosinophils circulate for about 8–12, up to 18 h at most, in the blood [7] prior to deposition in tissues. The expected AEC of a person ranges anywhere from 0 to 500 cells per microliter, the upper limit of normal being approximately 3–5% of cells. Peripheral eosinophilia is typically defined as more than 450–600 cells/mL of blood with arbitrary designations of mild > 500 cells/mL, moderate > 1500–5000 cells/mL, and severe > 5000 cells/mL [1]. Their exact quantity can vary within a single individual and can exhibit a diurnal variation with trough and peak levels occurring in the morning and late night, respectively, although this variation is mild and not thought to be clinically significant [8].

Eosinophils (greater than 90%) otherwise reside primarily in tissues, their numbers a hundredfold more abundant than in blood [9]. After circulation, they eventually migrate to the GI tract (the esophagus being the exception) among other mucosal-lined tissues, where they remain for at least a week, likely longer [10]. This happens independently of gut microbiota in the prenatal period [11] when eosinophil homing first occurs. Cytokines involved in the accumulation of eosinophils are numerous and include GM-CSF, IL-3, and IL-5 for growth, migration, and effector function; enhancement of endothelial adhesion via IL-1, 4, 13, and tumor necrosis factor α (TNF-α); and chemoattraction mediated by IL-5 [10]. Recruitment of eosinophils into the tissue requires CC chemokine ligand 11 (CCL11)/eotaxin produced constitutively by gut epithelial cells alongside eosinophil expression of CC chemokine receptor (CCR3) [10, 12]. These many molecules function in specific patterns to mediate eosinophil traffic.

Eosinophils can become activated in the setting of inflammation or other non-specific tissue insult. Under normal circumstances, eosinophils do not become pathologic. While they play a significant role in many disease processes, their normal biologic function is not yet precisely defined, though they likely have homeostatic immunoregulatory functions in concert with other components of the gut's immune system [13]. In a recent review, Weller et al. discuss the myriad functions of tissue-resident eosinophils, including in the gut where the absence of eosinophils is associated with decreased production of secretory IgA at the intestinal mucosa, alterations in the intestinal microbiome, and dysregulated mucosal barrier integrity [14]. Activation of the eosinophil is also incompletely understood, although one mechanism thought to occur utilizes immunoglobulin surface receptor crosslinking, to include IgA and IgG but not IgE, with human eosinophils expressing very low levels of high-affinity immunoglobulin receptor (FcεRI). In vitro, IL-5, interferon gamma (IFN-γ), others have also been used as agonists to activate eosinophils [15]. Activation in the tissues subsequently results in degranulation of preformed contents such as major basic protein, eosinophil cationic protein, lysosomal hydrolases, and eosinophil peroxidase [8], many of which have enzymatic activity that can be injurious to their human host [12]. These contents

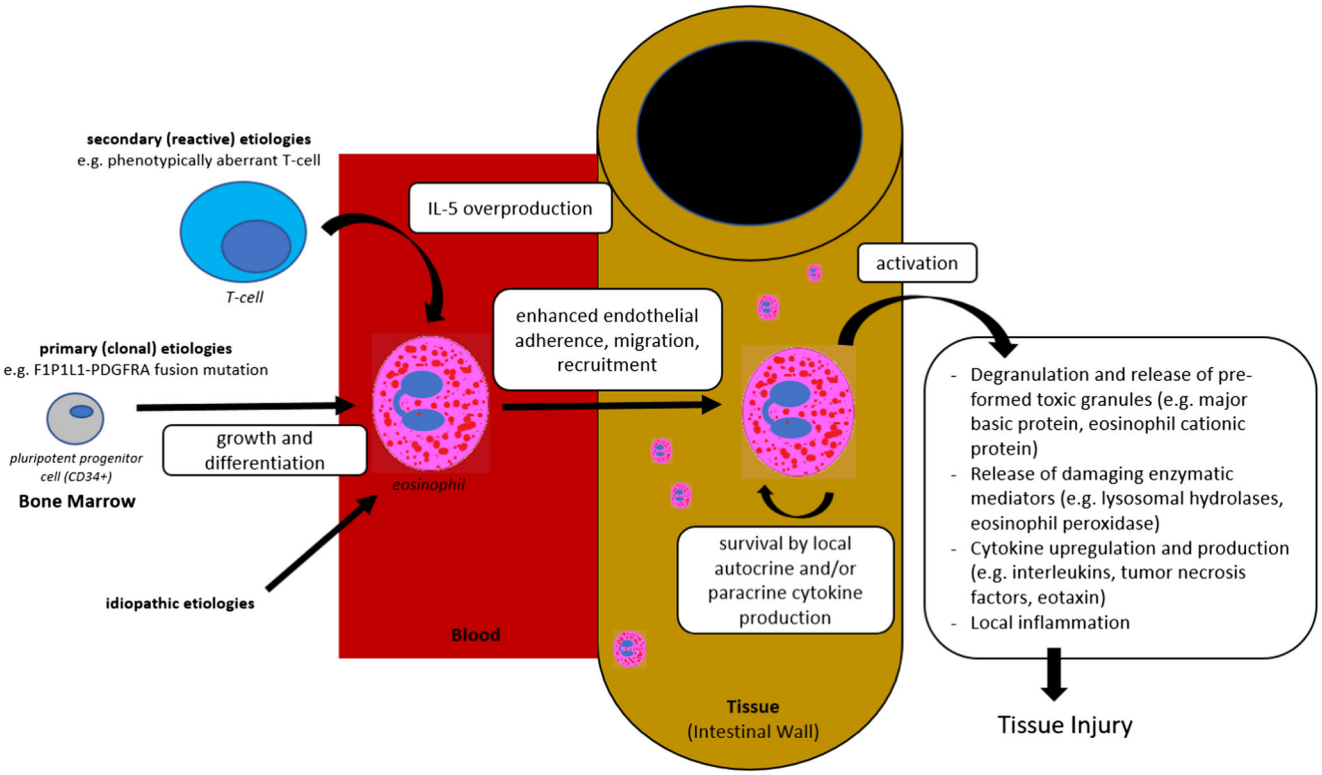


Fig. 1 Schematic of pathophysiologic concepts of gastrointestinal manifestations in hypereosinophilic syndromes, using the intestine as an example. End-organ damage occurs due to too many eosinophils infiltrating organ tissues

are contained in basic granules that classically bind acidic dyes (e.g., eosin) [16]. Activation also causes the eosinophil to newly synthesize and release lipids mediators, neuromediators, as well as upregulate cytokines (e.g., interleukins, TNFs, vascular endothelial growth factor (VEGF), eotaxin) [16]. Tissue damage from eosinophilia occurs from a number of methods, including release of toxic granules, cytokine production leading to tissue remodeling and fibrosis, and recruitment of inflammatory cells by lipid mediators. This theoretically occurs anywhere along the GI tract, from the oral cavity to the anus. Subsequently, eosinophils are not thought to recirculate into the blood. Once situated, their survival depends on the presence of local autocrine and/or paracrine cytokine production which, if lacking, will promote their apoptosis [15].

Clinical Manifestations and Presentation

The heterogeneous nature of HES can, not surprisingly, lead to a broad constellation of clinical signs and symptoms. As such, all gastrointestinal symptoms are theoretically possible, including abdominal pain, nausea, vomiting, diarrhea, and weight loss, all of which may be observed in almost all forms of HES [3]. Some of these symptoms can logically be associated with the anatomic area in question, such as dysphagia, food impaction, epigastric or chest pain, reflux-like symptoms, and even respiratory problems with esophageal infiltration, including feeding dysfunction in younger children, similar to that of eosinophilic esophagitis [17] whose symptoms eventually manifest due to fibrosis following chronic inflammation. In eosinophilic gastroenteritis, vomiting, abdominal pain mimicking acute appendicitis, diarrhea, melena, iron-deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive are associated with the mucosal (most common) variant. Bowel obstruction can result due to wall thickening if eosinophils infiltrate the muscularis layer. Serosal involvement appears characterized by exudative ascites and higher peripheral eosinophilia [6, 18]. The clinical symptomatology of eosinophilic colitis is poorly characterized, although diarrhea appears characteristic [19]. Lower intestinal involvement is described primarily in infants *without* peripheral eosinophilia as food protein-induced eosinophilic proctocolitis which presents classically as blood-tinged stool with absence of systemic symptoms in an otherwise well-appearing child [20].

While these manifestations are reported within the purview of EGIDs, gut-specific symptoms are not always exclusive to the location of eosinophilic infiltration in the GI tract, nor are they necessarily distinguishable between primary and secondary causes of hypereosinophilia. Symptoms also vary depending on the age of the patient, for example, poor growth in the pediatric patient [10]. Additionally, symptoms are non-specific and can be attributed to other non-eosinophilic

disease states, risking a delayed diagnosis. With regard to EGIDs, anywhere from 20 to 80% of eosinophilic gastroenteritis cases have peripheral eosinophilia; levels appear higher if the serosal layer of tissue is involved [18]. The incidence of eosinophilia with other EGIDs remains unknown, as EGIDs are generally thought to present without peripheral eosinophilia [21]; more specifically, eosinophilia is estimated to occur in less than 50% of all EGID patients [19]. Specific EGID entities associated with hypereosinophilia include the serosal form of eosinophilic gastroenteritis associated with ascites and eosinophilic colitis as referenced below. One 2011 retrospective review reported that in patients with EGID, greater GI segmental involvement was more likely with hypereosinophilia [22], although a strict linear relationship between symptoms and degree of eosinophilia remains unknown.

As previously mentioned, GI involvement is the third most commonly reported clinical manifestation in HES patients (up to 38%) [1]. It is also the third most common manifestation at initial presentation (14%) according to a large cohort published in 2009 [23]. At onset of HES, the two organ systems more commonly affected were the skin (37%) and lungs (25%) in the same cohort. The most serious complications, however, typically occur in the cardiac or nervous system [3], not the GI tract. HES presenting predominantly with GI symptoms is thought to be less frequent [24] as most of the clinical reports regarding eosinophilic infiltration of the gut are presented in the context of primary EGIDs. However, several cases of HES presenting primarily as gastrointestinal disease exist, to include patients with HES initially presenting with intractable gastric ulcers [25], bloating, diarrhea and weight loss [26], acute abdomen due to acute mesenteric artery thrombosis [27], gastroenteritis [28], colitis [24], resembling chronic inflammatory bowel disease with primary sclerosing cholangitis [29], acute perforation of the small intestine in the setting of EGPA [30, 31], sigmoid perforation in a patient with ulcerative colitis associated with HES [32], achalasia and hepatitis [33], liver masses [34], and even dysphagia and abdominal pain with eosinophilic infiltration of the oral cavity [35]. Nevertheless, it can be difficult to distinguish between "single-organ" or "overlap HES" (hypereosinophilic syndrome limited to involvement of a single-organ system, such as the gut), primary eosinophilic gastrointestinal disease states (EGIDs), and "reactive eosinophilia" manifesting as gastrointestinal eosinophilia, as in secondary causes such as medications. For example, we include a case of Crohn's disease in a 10-year-old boy who developed severe eosinophilic gastroenteritis and an AEC of up to 5120 after 1 year on infliximab and up to 3900 after 6 months of adalimumab [36], organ-restricted hypereosinophilia attributed to his medications not his or other primary GI disease states. Eosinophilia is associated with ulcerative colitis, but few data exist characterizing its role in the course of inflammatory bowel disease; however, a recent 2017 inflammatory bowel disease (IBD) cohort identifies the presence of peripheral eosinophilia as an at-risk subgroup for poorer clinical outcomes [37]. Some of the literature delineates HES from EGIDs by nature of, for the former category, (1) concurrent involvement of other organ systems (primarily skin, cardiac, and nervous system) and (2) higher risk of certain life-threatening complications (e.g., endomyocardial fibrosis [38]) although serious gastrointestinal complications from EGIDs do occur, such as a case of perforated duodenal ulcer in a patient with eosinophilic gastroenteritis [39]. Peripheral eosinophilia is more likely to be associated with HES than EGIDs [38] although cases of EGIDs reaching AEC > 1500 exist. It has been reported that there is a lower risk of bone marrow and cardiac involvement in EGID patients, although treatment and assessment for other associated end-organ damage is recommended regardless (see "Diagnostic Approach" and "Management" below) [40]. The incidence of all HES subtypes was estimated between 0.018 and 0.036 per 100,000 person-years, with a male-to-female ratio of 1.47 and a median age of 52.5 years at diagnosis [41]. The incidence of all EGIDs has not been calculated but is suspected to be rising. The incidence of eosinophilic esophagitis (EoE) was estimated at 4:1000 in an adult Swedish population and 1:1000 in children from Cincinnati, Ohio over 10 years [19]. Other epidemiologic data likely vary depending on the subtypes of both EGID and HES for which there remains a large paucity of information.

The clinical course of HES patients is dictated by the underlying mechanism. Tissue fibrosis remains the major concern given the potential for chronic inflammation if eosinophilia remains untreated, but why exactly this does not occur in all patients is not clear. Cases seemingly range from benign if clinically asymptomatic to fatal, with the more common causes of death involving cardiac dysfunction, infection, and untreated malignancy according to one 2013 retrospective review [42]. Entities which have been proposed to portend a worse prognosis include male sex, presence of a myeloproliferative syndrome (MPS) presence of cardiomyopathy, and poor response of hypereosinophilia to corticosteroids. Either an elevated B_{12} level (over five times normal) or the presence of splenomegaly is more likely associated with an MPS diagnosis [43]. In pediatric patients, major causes of mortality are also attributed to not only cardiac but also pulmonary involvement, not gastrointestinal involvement, of which only one of six children had hepatosplenomegaly with concurrent cardiac disease [44]. Two of 99 patients with "idiopathic eosinophilia" associated with clonal T cells developed cutaneous T cell lymphoma after 3–8 years of eosinophilia in recent study [45]. The myeloid variant HES subtype, which is associated with an elevated tryptase level, was found to portend a poor prognosis, tissue fibrosis, and favorable response to imatinib [46]. Other potential surrogate markers for end-organ damage have not been shown predictive between symptomatic and asymptomatic HES patients [47]. The prognosis of idiopathic HES

overall, however, appears generally favorable but is ultimately contingent on the extent of end-organ disease. A 5-year survival rate has been estimated at 80% [43]. There is no prognostic data reported specifically for gastrointestinal-associated HES.

Diagnostic Approach

When a patient presents with hypereosinophilia and GI symptoms, workup for the cause of the eosinophilia first needs to be sought. If eosinophilia and symptoms persist and no specific cause is identified, simultaneous workup for HES-related eosinophilia can be undertaken. The historical 1975 definition of HES with hypereosinophilia (> 1500 cells/mL) lasting greater than six consecutive months [48] has been considered outdated if only due to the need to treat patients with hypereosinophilic syndrome promptly (see "Management" below). It is suggested, in fact, that a comprehensive search not be delayed if hypereosinophilia has been sustained for over 1 month [49]. After hypereosinophilia is confirmed, ruling out secondary causes typically is recommended first [1, 5]. The differential for eosinophilia due to secondary causes is extremely large and a select listing is organized in Table 1 [8, 49]. These encompass any number of eosinophil-associated diseases and includes general categories of allergic disease, drug hypersensitivity (among the most common causes [5]) including "drug reaction with eosinophilia and systemic symptoms" (DRESS) syndrome, radiation exposure, infection (particularly parasitic, especially in developing countries, but *Helicobacter pylori* has also been reported [38]), neoplasms, certain metabolic diseases, connective tissue disorders, pulmonary disease, other systemic organic disease (e.g., immunodeficiencies such as autoimmune lymphoproliferative syndrome (ALPS) and hyper-IgE syndrome), systemic lupus erythematosus (SLE), EGPA, or IBD for which eosinophilia, albeit low, is a proposed negative prognostic factor [38], rare syndromes such as eosinophilia-myalgia syndrome and Gleich's syndrome, and organ transplant rejection [5, 38]. Strongyloidiasis is often given particular attention given the risk of fatal hyperinfection if corticosteroids are initiated [51]. Whether or not these diagnoses necessarily reach hypereosinophilic levels and/or the frequency thereof is unknown.

A more focused differential for gastrointestinal disease in the presence of eosinophilia is itself large and includes the various EGIDs (eosinophilic esophagitis, eosinophilic gastritis/gastroenteritis/enteritis, eosinophilic colitis) primary biliary cirrhosis, sclerosing cholangitis, eosinophilic cholangitis, hepatic eosinophilia secondary to drugs, or hepatic transplant rejection (Table 2). Workup for these causes is specific to the entity in question, supported first and foremost by a comprehensive and clinically appropriate history and physical

Table 1 General categories of secondary (reactive) eosinophilia with examples

Allergy
- Allergic bronchopulmonary aspergillosis
- Allergic rhinitis
- Aspirin-exacerbated respiratory disease
- Asthma
- Atopic dermatitis
- Chronic sinusitis (especially polypoid)

Autoimmune disease
- Beh et syndrome
- Bullous pemphigoid
- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Dermatitis herpetiformis
- Dermatomyositis
- Granulomatosis with polyangiitis
- IgG4-related disease
- Inflammatory bowel disease
- Sarcoidosis
- Sjögren syndrome
- Systemic lupus erythematosus

Chronic eosinophilic pneumonia

Cutaneous disease
- Kimura disease
- Schulman syndrome (eosinophilic fasciitis)
- Wells syndrome (eosinophilic cellulitis)

Drug hypersensitivity or toxicity
- Acute necrotizing eosinophilic myocarditis
- DRESS syndrome
- Interstitial nephritis
- Specific drugs can include: antibiotics, antiepileptics, antiretrovirals, allopurinol, ibuprofen

Endocrinopathies
- Addison's disease

Eosinophilic gastrointestinal disease (see Table 2)

Eosinophilia-myalgia syndrome

Immunodeficiency
- Autoimmune lymphoproliferative syndrome (ALPS)
- Hyper-IgE syndrome
- Omenn syndrome
- Wiskott-Aldrich syndrome

Infection
- Helminths (e.g., *strongyloides*, *toxocara)*
- Protozoa (isospora, dientamoeba, sarcocystis)
- Fungal (aspergillosis, coccidioidomycosis)
- HIV

Neoplasm
- Adenocarcinomas of the gastrointestinal tract
- Chronic myelomonocytic leukemia (CML)
- Hypereosinophilia–lymphoproliferative variant (L-HES)
- Lung cancer
- Lymphoma (T cell and Hodgkin)
- Squamous epithelium-related cancers
- Systemic mastocytosis
- Thyroid cancer

Organ transplant rejection

Radiation exposure

Modified from Kovalszki and Weller [50]

Table 2 Gastrointestinal diseases associated with eosinophilia

Eosinophilic gastrointestinal diseases (EGIDs)
• Eosinophilic esophagitis
• Eosinophilic gastritis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
Eosinophilic cholangitis
Hepatic eosinophilia
• Drug-induced (e.g., penicillin, tetracycline)
• Hepatic transplant rejection
Inflammatory bowel disease
Primary biliary cirrhosis
Sclerosing cholangitis

Modified from Kovalszki and Weller [50]

examination. This may include a rectal exam for potential pinworm infection, which has been shown to reach hypereosinophilic levels in two recent case reports of an adult and child [52, 53]. Broad evaluation for HES could include stool cultures and specific antibody testing for ova and parasites (e.g., *strongyloides and toxocara*) infectious investigation for HIV, assessment of the blood count for other cellular aberrancy, chemistries (including liver function testing, renal function), erythrocyte sedimentation rate, antineutrophil cytoplasmic antibodies, cardiac evaluation with troponin, echocardiogram, electrocardiogram, lung function with pulmonary function tests, computed tomography of the chest, abdomen, and/or pelvis, serum tryptase (which can be useful for ascertaining certain primary etiologies, see below), vitamin B_{12} level to investigate association with other hematologic disease states [54, 55], quantitative immunoglobulins including IgE, flow cytometry for lymphocyte phenotyping, and evaluation for clonal T cell receptor gene rearrangements. Given HES' predilection for cardiac, lung (up to 60% of patients have either cardiac or pulmonary manifestations [56]) and skin involvement, assessment of these systems should be pursued due to higher likelihood of morbidity and mortality if involved [57]. A multimodality imaging approach has been suggested to evaluate these patients, with magnetic resonance imaging being superior for particular evaluation of the gastrointestinal system [57]. Simultaneous assessment is performed for the evaluation of end-organ damage as much as it is to search for etiology. As always, however, such workup should be tailored to a patient's specific history and presentation to avoid unnecessary and ineffectual evaluation.

Importantly, tissue biopsy of an organ in question (in our case the gut) should confirm eosinophilic infiltration if clinically feasible as the gross endoscopic appearance may appear healthy [19] and biopsies will help to identify the organ at risk of damage. Tissue damage is generally thought to be more likely to occur when the AEC exceeds 1500/mL but also occurs at lower thresholds. However, there does not appear to be a direct correlation between the level of peripheral eosinophilia and the presence of clinical disease, as the degree of eosinophilia does not accurately predict the risk of end-organ damage [9]. Indeed, hypereosinophilia occurs in the absence of clinical manifestations [2]. There is no general consensus for what constitutes threshold cutoffs for hypereosinophilic infiltration of any parts of the gut, with the exception of > 15 eosinophils (eos)/hpf in cases of EoE [7]. A defined cutoff of 70 or greater eos/hpf in pediatric patients for eosinophilic gastritis was used in one descriptive study [58]. As previously mentioned, eosinophils are a normal part of the gut, and although normal values are yet to be established, eosinophils are generally believed to increase in quantity beginning from the stomach (with the esophagus normally devoid of eosinophils) down distally to the rectum, at least in pediatric patients [59], with baseline values ranging from a mean of 0.03 ± 0.1 eosinophils/hpf in the esophagus to the highest mean of 20.3 ± 8.2 eosinophils/hpf in the cecum most recently [60]. The pattern of normal eosinophil ranges in adults may be similar, with studies demonstrating healthy adult gastric counts at approximately < 38 eosinophils/mm^2 [61] and up to a mean of 45 ± 21 eosinophils/hpf in biopsies of normal ascending colon. The idea that normal numbers might also vary widely within each anatomic segment, let alone between them, however, makes quantification challenging. Levels additionally might have geographic and seasonal variation, with higher colonic counts found in patients from the southern USA [62] as well as higher eosinophil counts overall in patients during April and May [63], although this was not found to be statistically significant.

If secondary causes are excluded, workup for primary/additional neoplastic etiologies (Table 3) can be pursued, starting with screening for specific genetic mutations, particularly the FIP1LI-PDGFRA gene fusion mutation resulting from a 4q12 deletion. Obtaining a serum tryptase level is a useful surrogate marker if screening is not available since increased levels appear associated with myeloproliferative variants [1]. Other primary M-HES resulting from bone marrow dysfunction can be evaluated via cytogenetic analysis for reciprocal translocations including 4q12 (*PDGFRA*), 5q31-q33 (*PDGFRB*), 8p11-12 (*FGFR1*), and 9p24 (*JAK2*). Suggested subsequent evaluation if screens are negative include assessment for other clonal or molecular abnormalities (such as chronic eosinophilic leukemia which is distinguished by increased marrow blasts between 5 and 19%) or assessment for abnormal T cell function or phenotype (a.k.a. L-HES) as evidenced by immunophenotyping (the most commonly associated abnormal T cell population is the CD3-CD4+ T cell) or the presence of eosinophilopoietic cytokine overproduction in vitro (IL-5). Other genetic aberrancies causing hypereosinophilia include autosomal dominant familial eosinophilia mapped to chromosome 5q31-33 [64] where,

Table 3 Select categories of primary eosinophilias

• Acute or chronic eosinophilic leukemia
• Episodic eosinophilia with angioedema (Gleich's syndrome)
• Familial hypereosinophilia
• Hypereosinophilia–myeloproliferative variant (M-HES)
• Idiopathic hypereosinophilic syndrome

Modified from Kovalszki and Weller [50]

despite levels of eosinophilia reaching 5.292×10^9/L in some patients, many remain asymptomatic [65]. Bone marrow analysis is also recommended even if the peripheral blood indicates a neoplastic process as this could influence both diagnosis and/or prognosis.

Should none of the above be revealing, the diagnosis of "Hypereosinophilic Syndromes" can be given if end-organ damage is present, and the term "idiopathic hypereosinophilia" or "hypereosinophilia of undetermined significance" given if end-organ damage is absent. If no end-organ damage is found, patients need to be carefully monitored over time to prove that, in fact, no organ damage is about to occur or is asymptomatically occurring, with serial studies such as CT scans and labs as deemed appropriate. Figures 2 and 3 provide an overarching, general approach to the workup of gastrointestinal symptoms associated with hypereosinophilia. Overall, it may be obvious that exhaustive diagnostic workup may be delayed until after an acutely symptomatic patient is clinically stabilized with empiric therapy (see below).

Management

The overarching goal of therapy for all hypereosinophilic syndromes is to prevent and mitigate potentially irreversible end-organ damage. Treatment is specific to the underlying cause of potentially elucidated secondary etiologies. If the underlying mechanism is unclear (e.g., eosinophilic gastroenteritis versus HES) due to significantly elevated eosinophil counts without extraintestinal involvement, one could consider a trial of exclusive hydrolyzed formula diet to see if eosinophilia and symptoms improve. (This makes primary EGID more likely than HES).

In patients with idiopathic HES, treatment frequently relies on corticosteroids as mainstay given an eosinophil's marked sensitivity to steroids due, in part, to inhibition of chemotaxis [66]. A dosage of anywhere from 40 mg/day of oral prednisone to 1 mg/kg of prednisone orally per day to 1 g of methylprednisolone for those more acutely ill has been suggested for the adult population, with intravenous administration for gastrointestinal patients as clinically dictated, although there are no standardized recommendations for either the dosing or duration of treatment. A dose of 2 mg/kg/day methylprednisolone was used as first-line treatment in children with idiopathic HES [44]. Corticosteroid use typically results in prompt eosinopenia, with most patients stabilizing within a week [67]. However, tapers typically need to be prolonged, over months, for treatment. Inability to reduce eosinophilia or development of a worsening clinical picture is a likely indication to add another agent. In a retrospective analysis, monotherapy with prednisone (median maintenance dose 10 mg/day) induced partial or complete responses in 85% of 188 idiopathic HES patients at 1 month, with duration ranging anywhere from 2 months to 20 years [23]. The ability to respond to glucocorticoids, however, can be predicted based on HES subtype, with myeloid and lymphocytic variants responding the worst compared to idiopathic HES, EGPA, and "single-organ HES" in a study utilizing only patients with PDGFRA-negative HES [68]. PDGRFA-positive patients are also described to be unresponsive to corticosteroids. As noted earlier, poor steroid response is proposed as a poor prognostic factor for both the adult and pediatric [44] population. If considering corticosteroids, empiric treatment with ivermectin has also been advocated for those with potential exposure to *Strongyloides*, albeit laboratory evaluation for disseminated parasitosis should not delay treatment [67]. Empiric use of albendazole normalized hypereosinophilic counts in three unexplained cases in Israel after negative workup [69].

Other non-steroid traditional therapies have included hydroxyurea, IFN-α, methotrexate, cyclosporine, and imatinib mesylate. In the same retrospective study, monotherapy with hydroxyurea achieved complete response in 33% of patients, 17% with IFN-α monotherapy, and 1 of 5 patients using monotherapy with cyclosporine. Response to imatinib (400 mg daily) if FIP1L1-PDGFRA-positive has been well-documented and is considered the treatment of choice in these patients, with molecular remission reaching nearly 100% within a month. If there is any evidence of endomyocardial damage with elevated troponin or imaging suggestive, concurrent corticosteroids should also be used with induction therapy with imatinib. Unfortunately, utilization of the other aforementioned therapies is limited by toxicities, medication intolerance, as well as inability to be used acutely [5]. Acute therapies in patients unresponsive to steroids include vincristine with concurrent glucocorticoid [70] and hydroxyurea (500–1000 mg daily) although the latter may take up to 2 weeks to respond. Other second-line agents have included cyclophosphamide and etoposide. At the time of this article, imatinib mesylate remains the only pharmacotherapeutic agent Food and Drug Administration (FDA) approved specifically for treatment of HES in the appropriately selected population (myeloid features, PDGFR+ mutational analysis). A recent paper found that even in PDGFR-myeloid HES (greater

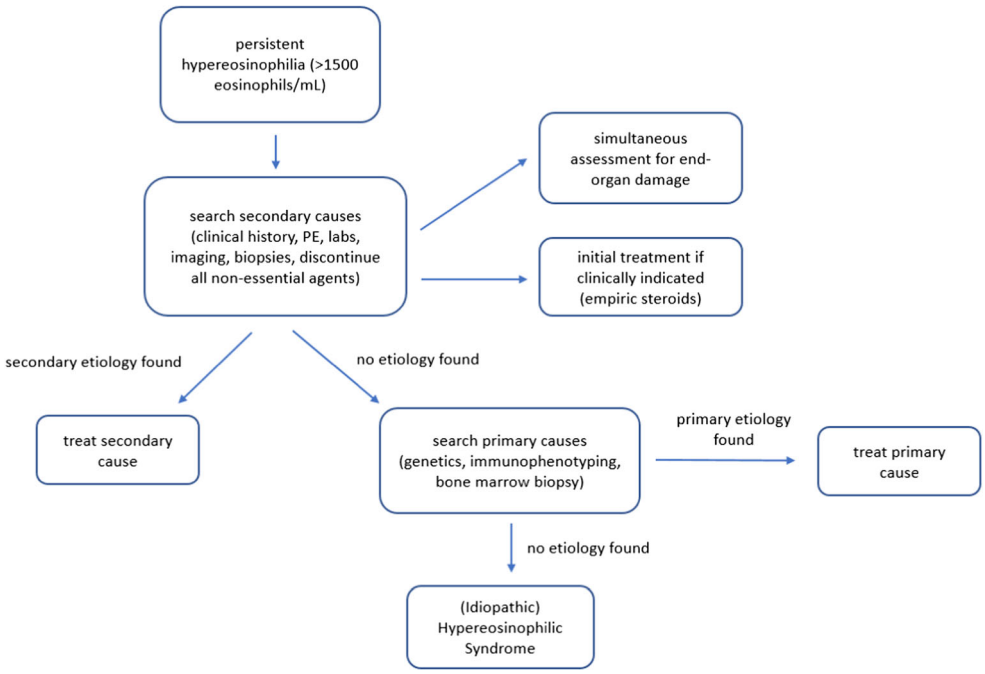


Fig. 2 Diagnostic approach for a patient with gastrointestinal symptoms and hypereosinophilia. No specific mechanism is found despite comprehensive workup in 70–80% of patients [6]

than or equal to four specific features needed), imatinib response can be seen in up to 54% of patients [71]. L-HES patients tend to necessitate chronic use of corticosteroids to maintain remission along with another agent (usually IFN-α). Steroid-sparing agents such as hydroxyurea and methotrexate which are also used in HES are usually given along with a glucocorticoid at a tapered dose.

Humanized monoclonal anti-IL-5 (mepolizumab) and anti-CD52 (alemtuzumab) antibodies have also been evaluated in HES patients albeit remain investigational and unlike imatinib

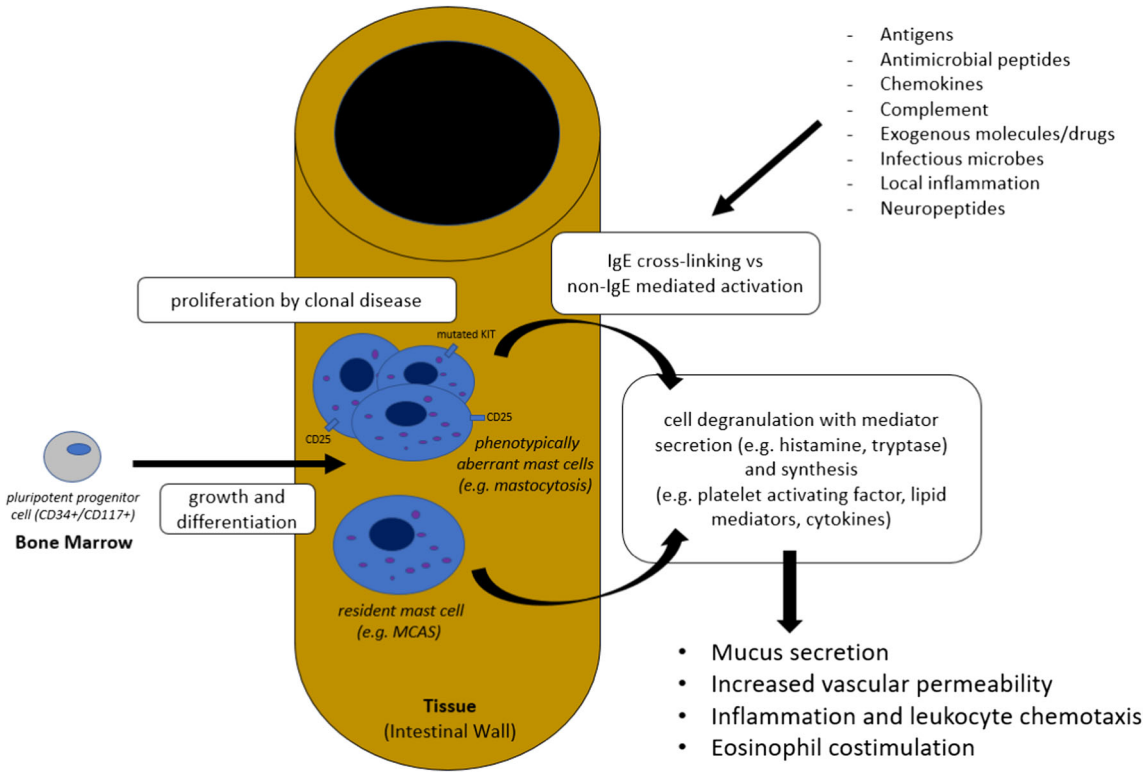


Fig. 3 Schematic of pathophysiologic concepts of gastrointestinal manifestations in mast cell disease. Symptoms occur due to release of mediators from mast cells

are not FDA-approved. Mepolizumab shows great promise: in a 2009 NEJM published trial on the effect of 750 mg IV dosing of mepolizumab in idiopathic HES (which included subtypes) and steroid-sparing effect (baseline on 20–50 mg of steroids), over 80% of patients tapered to less than 10 mg/daily prednisone [23]. In those who responded with steroid-sparing effect, L-HES necessitated the highest steroid dosing, and a 2010 paper subgroup analysis revealed that this higher dosing was needed to maintain an AEC of < 600 in these patients [72]. Mepolizumab is currently available for compassionate use in life-threatening HES [73]. There is currently a phase 3 prospective trial enrolling idiopathic HES patients for mepolizumab at the 300-mg subcutaneous dosing, FDA-approved in EGPA [ClinicalTrials.gov Identifier: NCT02836496]. Other upcoming biologics include anti-IL-5Rα (benralizumab) for which a phase 2 study has completed enrollment [ClinicalTrials.gov Identifier: NCT02130882] and anti-Siglec-8 [74]. These are exciting developments and less toxic therapies, targeted more specifically for eosinophils, with the hope of approved therapies in the anti-IL5 biologic realm soon for these hard-to-manage syndromes. Anti-IL5 therapies in EGIDs (specifically EoE) have been investigated but have not been generally successful in meeting their endpoints. While efficacious in reducing peripheral and potentially tissue eosinophilia (to a certain degree), they often did not fully relieve symptoms or organ damage. This is likely due to the underlying fibrosis seen in EoE patients [75, 76]. The role of transplantation in HES has not been fully investigated.

With specific regard to gastrointestinal symptoms, an initial 1988 case of a near-fatal eosinophilic gastroenteritis with systemic vasculitis patient was reported to respond only to oral sodium cromoglycate [77]; subsequent reviews have reported efficacious use of oral cromolyn therapy with regard to gastrointestinal eosinophilic infiltration in the setting of protein-losing enteropathy and food allergy [78, 79]. However, a retrospective review described 14 patients treated with oral cromolyn 100 mg QID for EoE and showed no improvement in clinical symptoms or tissue eosinophilia [80].

Generally, prompt therapy should be initiated with elevated levels (e.g., AEC $> 1.5 \times 10^9$/L) if any evidence of serious complications and end-organ damage exists [67]. Because end-organ damage could potentially develop at any time, it has been recommended to monitor for development of occult disease with troponin levels, chemistries, echocardiogram, and pulmonary function testing every 6–12 months, with assessment every 6 months for progression of already implicated organ involvement [64, 67]. However, the duration of such periodic monitoring remains unclear, especially in symptomatically quiescent patients, as the degree of eosinophilia does not necessarily correlate with either symptoms or end-organ disease.

Therapy for EGIDs in general is aimed at both symptomatic and histologic remission while maintaining nutrition and quality of life. Although treatment goals include both symptom improvement as well as endoscopic reversal of tissue pathology, they do not always correlate. Currently, there are no FDA-approved medications recommended specifically for treatment of EGIDs. Corticosteroids again appear to be mainstay for all, with a 2-week systemic course (about 20–40 mg daily) and subsequent taper used for acute exacerbation of symptoms. Regardless of what region of the gut is involved, improvement within 2 weeks is usually seen, although reports of its effectiveness are largely limited to case reports. However, relapse occurs once discontinued. Swallowed (topical) steroids in EoE induce remission in anywhere from 50 to 90% of patients but have not been found useful for more distal EGIDs [81]. Therapy is limited by side effects if needed over an extended period. Short-term use is considered relatively safe with the exception of oral or esophageal candidiasis occurring in up to 10% of patients [82]. In addition to steroids, withdrawal of suspected culprits, such as a food or drug, remains critical if applicable.

For eosinophilic esophagitis, the most prevalent EGID (estimated at 0.4% in Western countries [81]) non-steroid treatment options include dietary manipulation or potentially operative intervention (e.g., balloon dilation) if irreversible fibrosis with strictures and/or obstruction have occurred. A combination of dietary management with topical steroids is often utilized; however, no controlled studies directly comparing the superiority of dietary management to topical steroids currently exist, and compliance rates for use of either diet and steroids are poor (around 30% for both) [83]. Many recommend concomitant uses of a proton pump inhibitor regardless of what options are utilized, if at least for symptomatic relief [84]. Regarding dietary manipulation, some empiric four- and six-food elimination diets (EEDs) and testing-directed elimination diets (TDEDs) based on type 1 hypersensitivity testing yield about a 72% effectiveness for EEDs but only ~45% effectiveness for TDEDs, respectively, for *histologic* remission in a recent meta-analysis including both children and adults with EoE [85]. The most common foods identified include milk, egg, wheat, and soy. Interestingly, a 68% remission rate was found using milk elimination alone. The most extreme form of dietary manipulation comes in the form of drinking elemental formulas, which showed an efficacy rate of > 90% in the same study. Overall, food allergy testing-based elimination diets induce histologic remission in less than 1/3rd of adult patients; this number reaches about 50% in children. Biologic therapy for the treatment of EoE remains investigational: both reslizumab and mepolizumab have shown decreases in eosinophilic quantitation in both adults and children but no difference in clinical response compared to placebo. Neither infliximab nor omalizumab has so far shown changes in tissue eosinophilia or symptoms. Food oral immunotherapy induces EoE in up to 10% of patients. Aeroallergen

subcutaneous immunotherapy has been associated with symptom improvement in some cases of EoE [82].

Mast Cell Disorders

"Mast cell diseases" manifesting with gastrointestinal problems encompass several clinical entities, ranging from systemic mastocytosis to, potentially, functional GI disease. Diseases with mast cell (MC) involvement in general can be described as "primary" (clonal mast cell disorders, such as mastocytosis), "secondary" (such as from IgE-mediated anaphylaxis), or "idiopathic" in which no primary or secondary etiology is found. Mast cells have also been implicated to contribute to symptoms in other GI disorders such as gluten-sensitive enteropathy aka celiac disease, IBD, and irritable bowel syndrome (IBS). We focus primarily on mast cell infiltration of the gut with respect to some of the above diagnoses in this half of this review.

Pathophysiology

Like eosinophils, mast cells are tissue-resident cells that function normally within gastrointestinal immunobiology. Mast cells in the gut specifically account for 2–5% of mononuclear cells in the lamina propria [86] with a wide range of normal distribution. In a group of 100 asymptomatic patients, the mean mast cell density/hpf from colonic biopsies was 19 (range 7–39) [87]. Human mast cells derive from CD34+/CD117+ pluripotent precursors in the bone marrow and develop via activation by phosphorylation and dimerization of KIT/CD117 by stem cell factor (SCF or KIT ligand). They circulate in the bloodstream as mast cell progenitors and terminally differentiate after migration into many different tissues (e.g., lungs, skin, GI tract) in response to local cytokines that appear to be tissue-specific. Migration into the intestine appears to be mediated by CXCR2 and $\alpha 4\beta 7$ expression on mast cell progenitors alongside mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression on the gut endothelium, a process overall regulated by T-bet expression on dendritic cells [88]. Mature mast cells are found predominantly around blood vessels and nerves and contain preformed granules that bind basic dyes. These granules store mediators such as histamine and enzymes such as acid hydrolases, carboxypeptidase, cathepsin G, and neutral proteases. These neutral serine proteases comprise the majority of components inside the granule and include chymase and specifically tryptase which is unique to the mast cell [12]. Three phenotypes have been identified according to their protease content, including MC_T, MC_{TC}, and MC_C mast cells containing tryptase only, chymase only, or both. While the latter two phenotypes are classically found in mucosal surfaces such in the airways and connective tissues such as in skin, the MC_C phenotype is rare and can be found in the gut [89]. In addition to constitutive resident mast cells, both mast cell expansion and reversible expression of MC phenotypes in gut mucosa can occur in response to parasitic infections [90–92]. Mast cells can exhibit a significant variety of functional and structural differences both between and within organ systems and as such can exhibit variation in their methods of activation, mediator content, receptor expression, and ability to respond to pharmacotherapy [89]. Certainly, this may account for such clinical heterogeneity. Mast cell survival depends on the continued presence of SCF through FOXO3a inactivation and downregulation of Bim protein [88] and mast cells can live on average for weeks to months in tissues [12]. Apoptosis of human mast cells can occur via tumor necrosis factor-related apoptosis-inducing ligand-receptor (TRAIL-R) crosslinking [88].

Mast cells cause clinical manifestations via secretion of mediators following their activation. The mechanism of mast cell activation best described occurs after antigens bind to IgE and cross-link high-affinity FcεRI molecules on the mature mast cell, leading to subsequent signaling cascades. Importantly, non-IgE-mediated mast cell activation occurs as well via a large host of compounds: neuropeptides (including substance P, somatostatin, vasoactive intestinal peptide, and corticotropin releasing hormone (CRH) antimicrobial peptides, chemokines (including those produced by the mast cell itself), constituents of complement (C3a, C4a, C5a), toll-like receptor ligands, IgG1, exogenous molecules and drugs (such as those containing a tetrahydroisoquinoline motif), and even infectious pathogens themselves [12, 93]. Activation not only results in degranulation but also causes the mast cell to begin production and secretion of other molecules, specifically platelet activating factor (PAF), lipid mediators (PGD2, LTC4, LTD4, LTE4), and a multitude of cytokines including TNF and various colony-stimulating factors like GM-CSF. These mediators cause a variety of effector functions including bronchoconstriction, mucus secretion, increased vascular permeability, leukocyte chemotaxis, mast cell proliferation, inflammation, as well as eosinophil production [12]. The role of mast cells in pain has also been an active area of interest given their proximity to nerves and their ability to secrete neuropeptides [94]. Mediators that have been attributed specifically to gastrointestinal symptoms include histamine, PGD2, PAF, serotonin, tryptase, leukotrienes, TNF-α, and IL-6 [95].

Systemic mastocytosis (SM) is a neoplastic proliferative disease of mast cells associated with gain-of-function point mutations in KIT (typically D816V in more than 90% of adult cases) that aberrantly activates KIT's tyrosine kinase domain and autophosphorylates without SCF [96]. Other rare KIT mutations in mastocytosis include D816Y, D816F, D816H,

E839K. D820G, V560G, F522C, E829K, V5301I, and K509I, present in < 5% of mastocytosis patients, with different mutation patterns potentially dictating mastocytosis subtypes and response to therapy. This constitutive activation is associated with aberrant expression of CD25 and CD2, the former being more specific, which is used as a diagnostic criterion for SM. The inability of mast cells to undergo apoptosis has also been proposed as a pathogenic mechanism in mastocytosis given that constitutive expression of anti-apoptotic proteins have been found in bone marrow cells of SM patients [97].

Clinical Manifestations and Presentation

Like HES, dysfunction of the gastrointestinal tract in mast cell disease can manifest with non-specific gastrointestinal symptoms. "Mastocytosis" as a heterogenous group of disorders can range from affecting the skin only (i.e., cutaneous mastocytosis or urticaria pigmentosa) to systemic multi-organ involvement, including involvement of the gut; these include subgroups such as indolent, smoldering, aggressive, and those associated with hematologic neoplasms or mast cell leukemia. Symptoms in systemic mastocytosis largely result from release of mediators resulting in hypermotility, bloating, diarrhea, abdominal pain, nausea and vomiting, peptic disease, and in rare advanced cases infiltration of the gut interfering with absorption. Typically, symptoms are episodic in nature, as symptoms caused by mast cell activation can be distinguished by their discontinuous nature, reflecting the pattern of mediator release [93].

Systemic mastocytosis as a disorder of clonal proliferation of atypical mast cells can manifest with mast cell infiltration of theoretically any part of the gastrointestinal tract. In a survey of 420 patients with mast cell disorders, diarrhea was the most common gastrointestinal symptom reported by 66% of respondents [98]. This is seen across multiple studies, where both bloating and diarrhea are common manifestations with a mean occurrence of about 43% [99, 100] and up to 80% of patients experienced diarrhea and/or abdominal pain in an older 16-case prospective study [101]. Nine of these patients also had duodenal ulcers, with subsequent ulceration and severe duodenitis if left untreated. A more recent French study has also suggested a higher incidence of duodenal ulcer history in mastocytosis patients [100], and it has been postulated that elevated levels of histamine results in hypersecretion of gastric acid, thereby leading to peptic ulcer disease with an incidence higher than the general population [99]. The mechanism underlying SM-related diarrhea has not been fully investigated, although non-D816V KIT mutations appeared more associated with diarrhea than their D816V counterparts in the French study [100], and a mechanism of PGD2-mediated hypermotility has been suggested to explain this. Other GI signs and symptoms include abdominal pain, reflux, nausea, vomiting, malabsorption, weight loss, steatorrhea, and even GI bleed, with anywhere from 60 to 80% of SM patients experiencing some form of gastrointestinal symptomatology [99, 102] precipitated by the same mediators that can cause other clinical manifestations of SM. Known SM presenting with acute appendicitis as a manifestation has also been reported whereby histologic assessment of the inflamed appendix revealed notable mast cell infiltration (> 30 mast cells per high-power field) [103]. Histologic lesions otherwise (see "Diagnostic Approach" below), however, have not always been found to correlate with clinical symptoms [100]. Overall, GI symptoms were reported as the most distressful aspect of the disease by 18% [98].

While most patients with systemic mastocytosis have the indolent subtype associated with normal life expectancy, rare patents may present with aggressive systemic mastocytosis with GI tract involvement such as malabsorption, hypoalbuminemia, and weight loss. Liver involvement is rare but can also occur in aggressive systemic mastocytosis (ASM) and manifest with portal hypertension and ascites. Laboratory findings in ASM with liver involvement may include elevated transaminases, hyperbilirubinemia, and elevated alkaline phosphatase, although isolated alkaline phosphatase elevation is common in indolent disease and should not be considered a sign of ASM. Patients with smoldering systemic mastocytosis (a transitional category between indolent and aggressive systemic mastocytosis) may present with hepatomegaly but with no signs of liver dysfunction. Gastrointestinal manifestations are also commonly seen in non-clonal (secondary or idiopathic) mast cell activation syndromes [104].

Mast cells have been implicated in the pathophysiology of diarrhea-predominant IBS patients given findings of increased numbers of mast cells in the ileum, jejunum, and colon of these patients. These patients are also showing higher basal stress levels compared to healthy controls [87, 105]. The close proximity of mast cell degranulation to colonic innervation has also been demonstrated, potentially helping to explain the abdominal pain experienced by IBS patients [106], even if the overall density of mast cells can be similar to that in the gut of healthy patients [87]. IBS symptoms are frequently provoked by external triggers such as food and stress, which can also provoke non-IgE-mediated mast cell release. Blockage of acute stress-induced intestinal permeability by disodium cromoglycate (DSCG) in humans suggests a role for mast cell stabilizers in the treatment of IBS [107, 108]. Overall, however, it is difficult to distinguish between where physiology ends and pathology begins, as gastrointestinal mast cells

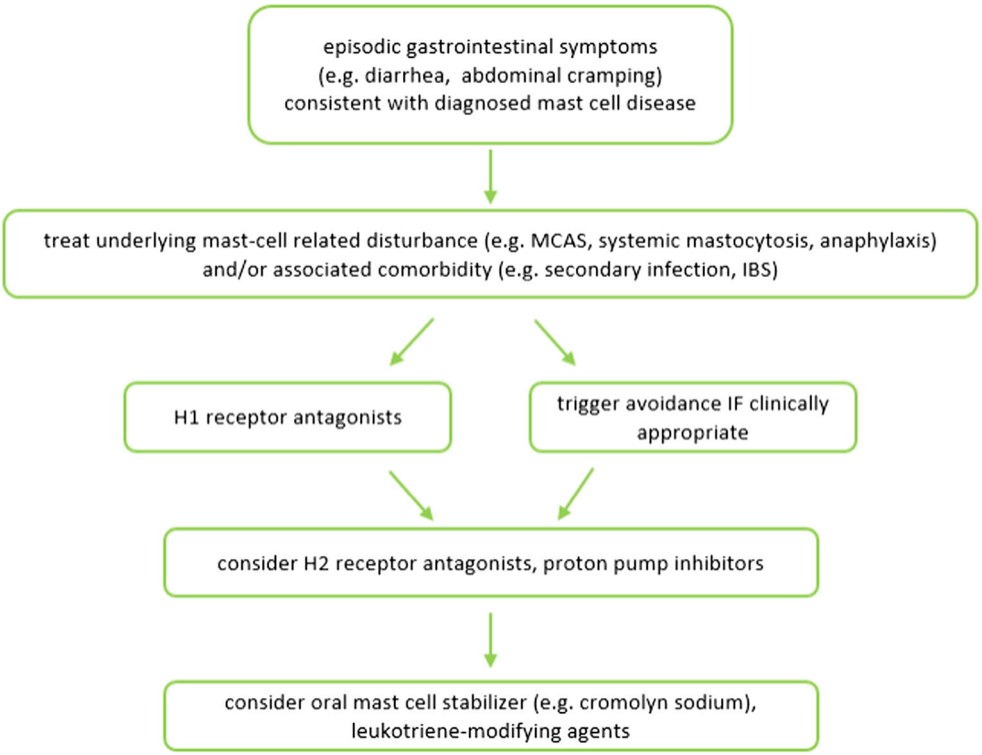


Fig. 4 Possible stepwise management for a patient with gastrointestinal symptoms and mast cell disease. Other interventions reported in the literature and not necessarily systematically studied include: low-histamine diets, FODMAP diet, corticosteroids, omalizumab, and cytoreductive agents

degranulate normally to help regulate permeability, secretion, peristalsis, and serve as important constituents of gut innate and adaptive immunity [109].

Diagnostic Approach

Patients suspected of having gastrointestinal disease resulting from underlying mast cell infiltration usually arise in those with already known diagnoses of mast cell disease. The presence of associated cutaneous and bone marrow disease helps direct investigation. The greater challenge lies in identifying an underlying mast cell etiology for patients presenting with isolated GI symptoms. This challenge is already made difficult not just due to the heterogeneity of gastrointestinal presentations but also the unclear role of the mast cell in other gastrointestinal disorders and lack of diagnostic criteria for mast cell entities other than mastocytosis and "mast cell activation syndrome" (MCAS). In general, biopsy remains a critical diagnostic step through which further workup can be guided.

For those symptomatic GI patients suspected of having mastocytosis, the workup is clearer. A serum tryptase level reaching > 20 ng/mL is highly suggestive of an underlying mast cell disorder, and bone marrow investigation with assessment for a KIT mutation is recommended to ascertain diagnostic criteria and further staging assuming that the rest of the clinical history also fits [110]. While a serum tryptase level is typically used as a surrogate marker (and hence screen) for mast cell involvement, a normal tryptase does not rule out primary disease, making biopsy essential. Biopsies must be stained with the appropriate markers including tryptase, CD117, and CD25. While tryptase is the most specific mast cell stain, it can be uniquely absent in some GI mast cells and therefore CD117 stain should be performed. Expression of CD25 in tryptase or CD177 positive mast cell clusters in the gut confirms the diagnosis of mastocytosis. Patients with GI involvement always have systemic mastocytosis demonstrable in a bone marrow biopsy.

Monoclonal mast cell activation syndrome (MMAS) benefits from pathologic assessment as it is defined as meeting only one or two minor criteria for SM [111]. The term MCAS is described as an entity that presents with symptoms manifesting in two or more systems, including the GI tract. Diagnosis requires (1) remission of symptoms in response to anti-mediator therapy and (2) meaningful elevation of a validated mast cell mediator such as baseline tryptase of 20% + 2 ng/mL during or within 4 h of being symptomatic or 24-h urinary elevations in urinary *N*-methylhistamine, PGD2 metabolites, or LTE4 [96, 97, 104]. Therefore, the role of GI manifestations in making a diagnosis of MCAS is significant only if there is a response of these symptoms to anti-mediator therapy in the setting of demonstrated underlying mediator abnormalities consistent with the criteria for diagnosing this disorder. Of note, serum tryptase level appears to reflect the total body's

mast cell burden and is influenced by the number of alpha tryptase genes expressed [94] so interpretation of a tryptase level must always be done with care. Familial hypertryptasemia is an autosomal dominant condition found in 6% of the general population involving the *TPSAB1* gene. These patients have elevated tryptase levels at baseline but there is no data to suggest that the mast cells of these patients are any more active than those with normal tryptase levels [104]. This diagnosis can be suspected by obtaining baseline tryptase levels in family members of the index case and confirmed by genetic analysis; however, this only remains available on a research basis.

Given that mast cells are normally resident cells, their mere presence in the gut is not pathologic. Histologically, the presence of atypical intestinal mast cells can be subtle and difficult to identify. Mastocytosis in the gut has been characterized by the presence of associated eosinophils especially in the colon (Fig. 5a, b) and focal involvement necessitating multiple biopsy sites. In contrast, performing mast cell quantification to showcase infiltration for diagnoses other than SM is likely ineffective given the lack of characterization and likely variability of intestinal biopsies for many diseases in which the role of mast cells has been implicated. Indeed, empirically obtaining colonic mast cell counts during workup of patients with chronic diarrhea, for example, has not been shown to be helpful [112] despite previous findings of increased mast cell numbers in patients with diarrhea-predominant IBS [105]. Cutoffs have been suggested to indicate abnormal infiltration (e.g., 20 mast cells/hpf in gut lamina propria) though this has not been supported by other studies [86]. A recent comparison between 200 colonic biopsies from either asymptomatic or IBS-diagnosed patients instead showed significant overlap [87]. The term "mastocytic enterocolitis" has been coined to described rare cases in which chronic, intractable diarrhea was attributed to increased mast cell infiltration found in biopsy specimens with resolution following antihistamine therapy after exhaustive negative workup [113, 114]; as already mentioned, however, the relationship between mast cells and these entities remains unclear.

Between biopsies, serum and urinary markers, and empiric therapy, no further approaches are yet described to help practitioners investigate the presence of mast cell activity in a patient with GI symptoms. If these otherwise fail to establish mast cell involvement, non-mast cell disorders should be considered.

Management

Treatment relies on the underlying cause of mast cell-related GI disturbance. Treatment for advanced mastocytosis including aggressive systemic mastocytosis with heavy gut infiltration and malabsorption and liver disease includes cytoreductive agents which reduce mast cell burden such as midostaurin, alpha-interferon, and cladribine and is otherwise beyond the focus of this review. Symptomatic treatment of mast cell mediator symptoms of gastrointestinal disease relies on anti-mediator therapy with predominantly antihistamines [95, 110]. Uses of H_1 and H_2 receptor antagonists are often combined, or a proton pump inhibitor is added to treat gastric disease. Cromolyn as a mast cell stabilizer (100–200 mg by mouth up to four times per day) has been shown efficacious for gastrointestinal manifestations in SM patients [115]. Low-dose corticosteroids have been reported to relieve malabsorption and ascites [116]. Other agents

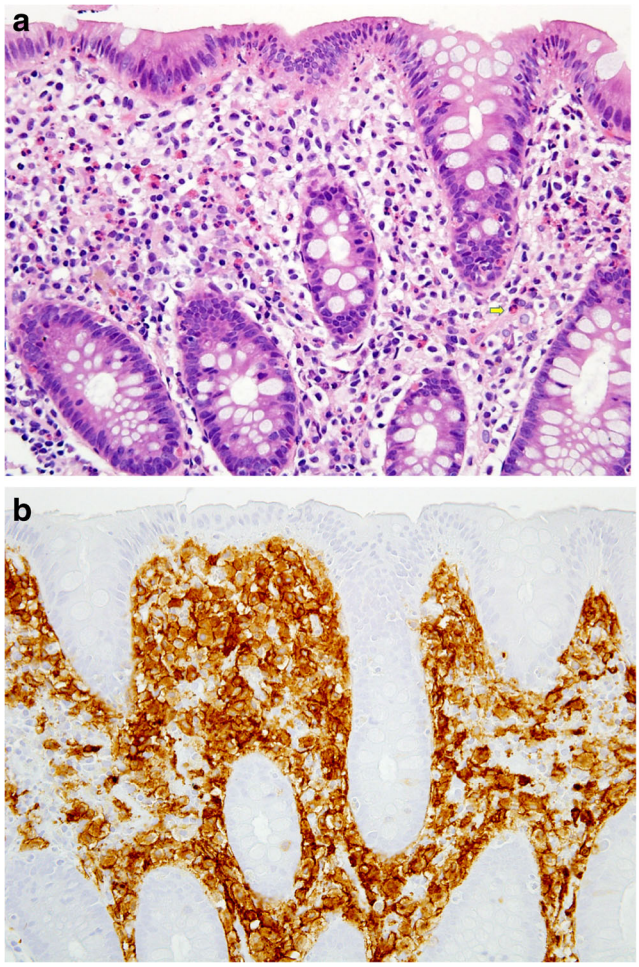


Fig. 5 **a**. H&E staining of a colon biopsy showing diffuse infiltration of mast cells in the lamina propria with increased scattered eosinophils (arrow). Magnification ×40. [Image used with permission from Jason L. Hornick, MD, PhD., Professor of Pathology, Harvard Medical School, Director of Surgical Pathology and Immunohistochemistry, Brigham & Women's Hospital, Boston, MA]. **b** CD117 (KIT) immunohistochemical staining of the same colonic biopsy highlighting the compact mast cell infiltrate. Magnification ×40. [Image used with permission from Jason L. Hornick, MD, PhD., Professor of Pathology, Harvard Medical School, Director of Surgical Pathology and Immunohistochemistry, Brigham & Women's Hospital, Boston, MA]

suggested to help treat "overactivation" of mast cells without particular mention of GI symptoms include leukotriene antagonists and omalizumab [104]. Oral budesonide has been used in sporadic cases but there are no systematic studies regarding its efficacy. Agents are typically given in stepwise fashion alongside non-pharmacotherapeutic interventions such as trigger avoidance and stress management if appropriate. Although studies show some improvement in IBS symptoms with fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) diet restriction [117], dietary modifications for those with mast cell symptoms, such as with low-histamine diets, have not been studied. One possible stepwise algorithm for managing GI symptoms in mast cell disease is shown in Figs. 4 and 5.

Discussion

Eosinophils (eos) and mast cells (MCs) are key effectors of not only allergic conditions but also autoimmune, cardiovascular, and hematologic and oncologic disease states [118]. Eos and MCs do not necessarily function in isolation from each other but participate in bidirectional crosstalk. Both can be affected by similar mediators but more importantly also influence one another in a paracrine fashion, dubbed the allergic effector unit (AEU). Their interactions include production of soluble mediators for specific eos/MC receptors (e.g., eosinophil recruitment and activation by mast cells releasing histamine and eotaxin) and direct physical contact (e.g., costimulatory interaction between CD48 and 2B4) with a well-defined interface that can last for about 3–4 min [119]. In vitro, there has been observation of morphologic change and the physical transfer of cellular content (e.g., erythropoietin from eos to MCs and tryptase from MCs to eos) [120]. Mast cell presence was also seen to enhance eosinophil viability especially in the presence of SCF, and the interaction between both cell types can promote their activation [50, 121, 122]. In vivo, mast cell-eosinophil pairings are detected in gastric carcinomas, allergic rhinitis, asthmatic bronchi, and in murine atopic dermatitis. Given that eos and MCs are both resident cells of the gut, it seems unlikely that only one and not the other would be affected, in some way, during pathologic states.

The relationship between clonal forms of hypereosinophilia and systemic mastocytosis has also been explored. Molecular aberrancies identified responsible for each entity infrequently overlap but shared mutations do occur. A patient with concurrent chronic basophilic leukemia and systemic mastocytosis was found to have PRKG2-PDGFRB fusion, and subsets of patients with both elevated tryptase and eosinophilia were found to carry FIP1L1-PDGFRA (M-HES) [97]. Peripheral eosinophilia occurs in up to 28% of SM patients, and eosinophils also frequently dominate, if not obscure, the biopsies of patients with SM. However, these eosinophils do not seem to cause overt destruction in SM and typical mast cell symptomatology does not seem to manifest in HES. Why these cells act differently in HES and SM is not understood [123].

In gastrointestinal diseases such as EoE, both increased numbers of MCs and activated MC/eosinophil couplets are found in the biopsies of these patients [118, 124]. IL-9 is a cytokine allocated with many immunologic functions including an essential role in mast cell activation and maturation and is produced especially by EoE eosinophils. Mepolizumab therapy in pediatric patients with EoE decreased both eos and MC quantitatively, but only esophageal MC numbers correlated with symptom severity (whereas the reduction in eosinophils did not [125]). Reslizumab also reduced esophageal eos in pediatric patients but without clinical improvement [75]. This effect was not found after mepolizumab therapy in EoE adults. Whether or not mast cells and the concept of "esophageal mastocytosis" play necessary roles in EoE pathophysiology remains unanswered. Cases of concomitant mastocytosis and gastrointestinal esophageal infiltration by eosinophils have also been reported, as in a 20-year-old male who presented with both urticaria pigmentosa and esophageal eosinophilia (> 20 eos/hpf) with characteristic endoscopic features [126]. He did not have EoE symptoms, however. Our understanding of the joint role of MCs and eos also continues to evolve in other gastrointestinal disease states, particularly inflammatory bowel disease [127], although much of what is known appears to be based mainly on observations regarding increased cell and mediator quantity.

Conclusions

An overall theme of heterogeneity describes the pathophysiologic mechanisms and clinical characteristics for defined (or yet to be defined) disease states in which eosinophils and mast cells play primary roles. Diagnosis can be challenging given such overlap and the need for better targeted therapy remains. Gastrointestinal symptoms are of the most common and/or debilitating aspects of both HES and mast cell disease states. Given their frequent coexistence, shared mechanisms, and potentially complementary involvement, mast cells and eosinophils should not be thought of in isolation but perhaps together as a potential therapeutic strategy. Further investigation of eosinophil-mast cell interplay therefore might provide greater opportunities for advancement in both mechanistic understanding as well as treatment in the future for both allergic and non-allergic diseases alike.

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