

Classification of eosinophilic disorders of the small and large intestine

Aoife J. McCarthy^{1,2} · Kieran Sheahan^{1,2}

Received: 29 June 2017 / Revised: 19 September 2017 / Accepted: 18 October 2017
© Springer-Verlag GmbH Deutschland 2017

Abstract Eosinophilic gastrointestinal diseases (EGIDs), including eosinophilic gastroenteritis and eosinophilic colitis, have been increasing in prevalence in Western countries in recent years. Eosinophils are normally scanty in the gastrointestinal tract, and increased numbers of eosinophils can denote pathology. Normal values for tissue eosinophils vary widely between different segments of the colon, thus location of the biopsy is critically important for the interpretation of findings. However, no standard diagnostic criteria have been proposed for the diagnosis of eosinophilic gastroenteritis or eosinophilic colitis. Gut eosinophilia encompasses entities that are predominantly immunoglobulin E (IgE)-mediated, the primary EGIDs and those that are secondary and not IgE-mediated. A final diagnosis of eosinophilic gastrointestinal diseases requires careful pathological assessment, clinical correlation and exclusion of several differential diagnoses.

Keywords Colitis · Enteritis · Eosinophilic · Eosinophils · Gastroenteritis · Intestine

Background

Eosinophilic gastrointestinal disease (EGID), including eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC), have been increasing in prevalence in Western countries in recent years. Histological examination of endoscopic biopsies

plays an important role in making a definitive diagnosis of EGID, and pathologists must take into account the normal number and distribution of eosinophils in gastrointestinal tract (GIT) mucosa, when examining histological specimens from these patients.

There have been a number of recent reviews on the topic of EGIDs [1, 2]; this review concentrates on eosinophilic disorders of the small and large intestines.

Epidemiology of EGIDs

There is very little information on the epidemiology of EGIDs due to their relatively low prevalence. Most of the knowledge relating to these disorders has been acquired from isolated case reports of different ages, which makes it difficult to draw firm conclusions and reach a consensus to establish diagnostic criteria [3]. However, over the past few decades, there has been a sharp rise in the prevalence of EGIDs, as evidenced by the rapid growth in reported cases in numerous populations [4–6].

Eosinophils

Eosinophils are granulocytes, first described by Paul Ehrlich in 1879 [7]. In the bone marrow, progenitor primitive stem cells differentiate into eosinophilic precursor myeloblasts under the influence of interleukin (IL)-1, IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF) [8]. The terminal differentiation into eosinophils and any proliferation thereafter is critically dependent on the presence of IL-5 [9]. Eosinophils are predominantly tissue-dwelling cells, with greatest affinity for epithelial surfaces that interact with the external environment (e.g. GIT, skin, lung), with only a small

✉ Aoife J. McCarthy
aoifejmccarthy@hotmail.com

¹ Department of Histopathology, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland

² School of Medicine, University College Dublin, Dublin, Ireland

number of mature eosinophils circulating in peripheral blood [9].

In response to eotaxin, a chemokine that is constitutively expressed throughout the GIT, eosinophils migrate to the GIT.

Eosinophils are potent pro-inflammatory cells that produce and release several cytotoxic proteins, cytokines, reactive oxygen metabolites and leukotrienes. Their pro-inflammatory functions are involved mainly in protecting against parasites and allergies [10].

Identification of eosinophils

Eosinophils are readily recognized in both haematoxylin-and-eosin (H&E)-stained and Giemsa-stained tissue sections. The nucleus of eosinophils may appear small and uni-lobulated, or there may appear to be two minor nuclei, depending on the level at which the bi-lobated nucleus has been sectioned [11].

Some eosinophils can only be recognized by their distinctive eosinophilic cytoplasmic granules [11]. Degranulation can be a morphological correlate of activation, but eosinophil degranulation may also be induced by biopsy procurement and processing [12] (Fig. 1).

Eosinophils and cell-free granular structures in degranulation can be highlighted by immunohistochemistry using monoclonal antibodies against eosinophil major basic protein (MBP), eosinophilic cationic protein (ECP) and/or eosinophil peroxidase (EPO) [13–15].

Eosinophils in the gastrointestinal tract

Eosinophils are part of the normal structure of certain digestive tract organs (they are not usually present in the oesophagus), where they are more numerous than in other tissues.

There is only limited information regarding the normal eosinophil count or normal distribution of eosinophils in GIT mucosa, and there is no established consensus for the histological diagnosis of eosinophilic gastroenteritis or colitis [9, 16], therefore rendering morphological diagnosis of EGIDs quite subjective [17–21].

It is thought that the number of lamina propria eosinophils varies significantly depending on the geographic regions individuals come from, with differences by a factor of 40 being reported [22]. Their numbers may also differ seasonally, with reports suggesting greater numbers of eosinophils in the months of April and May [11, 18].

It has been shown that in the lamina propria of the GIT, eosinophils are more concentrated in the deep compared to the superficial lamina propria [23].

Eosinophils in the small bowel

It has been shown that in the small intestine, eosinophils are more numerous in inter-cryptal lamina propria when compared with intravillous lamina propria [19]. The normal ileum may show up to as many as 30 eosinophils/HPF [20] (Table 1).

Suggested criteria for the diagnosis of EGE include > 20 eosinophils/HPF, > 30 eosinophils/HPF and > 50 eosinophils/HPF [20, 24]. However, the most accepted definition is a count that exceeds at least 20 eosinophils/HPF in at least one sample [25–27] (Table 1).

In the duodenum, eosinophilia has been defined as > 22 eosinophils/5HPFs at the base of glands for adults [28] and > 10 eosinophils/HPF for children [20].

Any clustering, even of a few eosinophils, in the lamina propria, in the muscularis mucosae, or in the crypts of the small bowel is an abnormal finding [2].

Eosinophils in the large bowel

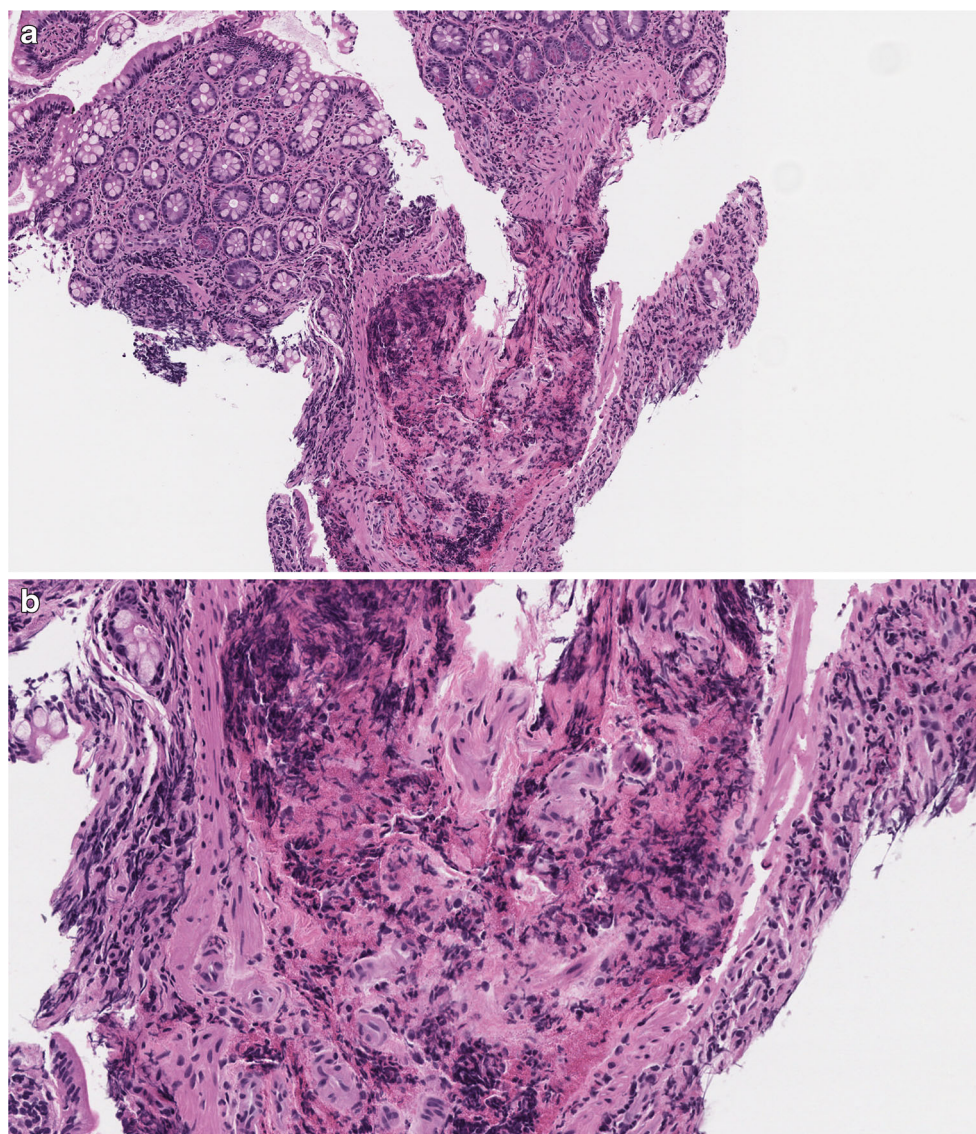
Lowichik and colleagues showed a mean of 17 eosinophils/HPF (and observed up to 52 eosinophils/HPF) in colons of individuals with no known gastrointestinal (GI) disease [20], while DeBrosse and others found up to 50 eosinophils/HPF in apparently normal colons [19] (Table 2) (Fig. 2).

It is known that eosinophils are concentrated mainly in the right colon (particularly in the caecum and appendix (11)—up to 30 eosinophils/HPF) with several studies showing a gradient of eosinophil density from proximal to distal large bowel [19, 20, 29]. Polydorides and colleagues reported that lamina propria eosinophils were, on average, three times more numerous in the ascending colon compared with the descending colon [18]. Similarly, Saad et al. reported a gradual decrease in the number of eosinophils in the lamina propria from the caecum to the descending colon, and, in addition, they showed another peak in the rectosigmoid colon [17] (Fig. 3). Thus, it seems that a cut-off value for eosinophil counts for rendering a diagnosis of EGIDs, should be individualized to the different biopsy sites, as relying on a single threshold for the entire colon can lead to inaccurate diagnostic assessments [16].

It has been stated that the term ‘eosinophilic colitis’ may be used if there are more than 15–25 eosinophils/HPF [9], with Lee et al. and Alfadda and colleagues using a threshold of 20 eosinophils/HPF [27]. Odze and others, however, used a threshold of > 60 eosinophils/10HPFs [30] to make a diagnosis of eosinophilic colitis (Table 2).

Recently, Turner and colleagues established the following thresholds for a diagnosis of eosinophilic colitis based on the site in the colon: > 50 eosinophils/HPF in the right colon, > 35 eosinophils/HPF in the transverse colon and > 25 eosinophils/HPF in the left colon [16] (Table 3).

Fig. 1 Biopsies from the ileum showing a marked increase in lamina propria and submucosal eosinophils (1a), with extensive eosinophilic degranulation (1b)



Diagnosis of EGIDs

As no widely accepted diagnostic criteria has been established for EGIDs, the diagnosis is dependent on the expertise of the histopathologist evaluating the biopsy samples. Differentiation of EGIDs from the normal condition relies on several factors,

namely [1] eosinophil quantification (and comparisons with normal values), [2] the location of eosinophils (e.g. their presence in abnormal positions such as intraepithelial, in the superficial mucosa, and within crypts), [3] the presence of extracellular eosinophilic staining constituents (often free granules) and [4] the absence of pathological features

Table 1 Normal number of eosinophils/HPF in the small intestine and suggested minimum eosinophil count/HPF for a pathological diagnosis of eosinophilic gastroenteritis

Category	Number of eosinophils/HPF	Authors
Normal number of eosinophils in the small intestine	Up to 30 eosinophils/HPF	Lowichik et al.
Suggested minimum eosinophil count for a pathological diagnosis of eosinophilic gastroenteritis	> 20 eosinophils/HPF	Uppal et al., Chen et al., Lee et al.
	> 30 eosinophils/HPF	Lowichik et al.
	> 50 eosinophils/HPF	Ingle et al.

HPF high power field

Table 2 Normal number of eosinophils/HPF in the large intestine and suggested minimum eosinophil count/HPF for a pathological diagnosis of eosinophilic colitis

Category	Number of eosinophils/HPF	Authors and location
Normal number of eosinophils in the large intestine	Up to 50 eosinophils/HPF	DeBrosse et al.; Cincinnati, USA
	Up to 52 eosinophils/HPF (mean 17 eosinophils/HPF)	Lowichik et al.; Texas, USA
Suggested minimum eosinophil count for a pathological diagnosis of eosinophilic colitis (see also Table 3)	15–25 eosinophils/HPF	Yan et al.
	> 20 eosinophils/HPF	Lee et al., Taiwan; Alfadda et al.
	> 60 eosinophils/10 HPFs	Odze et al.; Boston, USA

HPF high power field, HPFs high power fields

suggestive of other primary disorders (e.g. neutrophilia associated with inflammatory bowel disease (IBD), vasculitis associated with Churg–Strauss syndrome) [31].

Causes of eosinophilia in the small bowel and large bowel

Classification of EGID is complex due to difficulty in assigning aetiology in many cases, as clinical features,

morphology, localization, and site of manifestation often overlap in different GI diseases associated with eosinophilia [11].

Gut eosinophilia encompasses entities that are predominantly immunoglobulin E (IgE)-mediated, the primary EGIDs and those that are secondary and not IgE-mediated [32].

Primary EGIDs (comprising eosinophilic oesophagitis, eosinophilic gastritis, EGE, and EC) represent an unusual spectrum of inflammatory GI disorders in which eosinophils infiltrate the gut in the absence of known causes for such

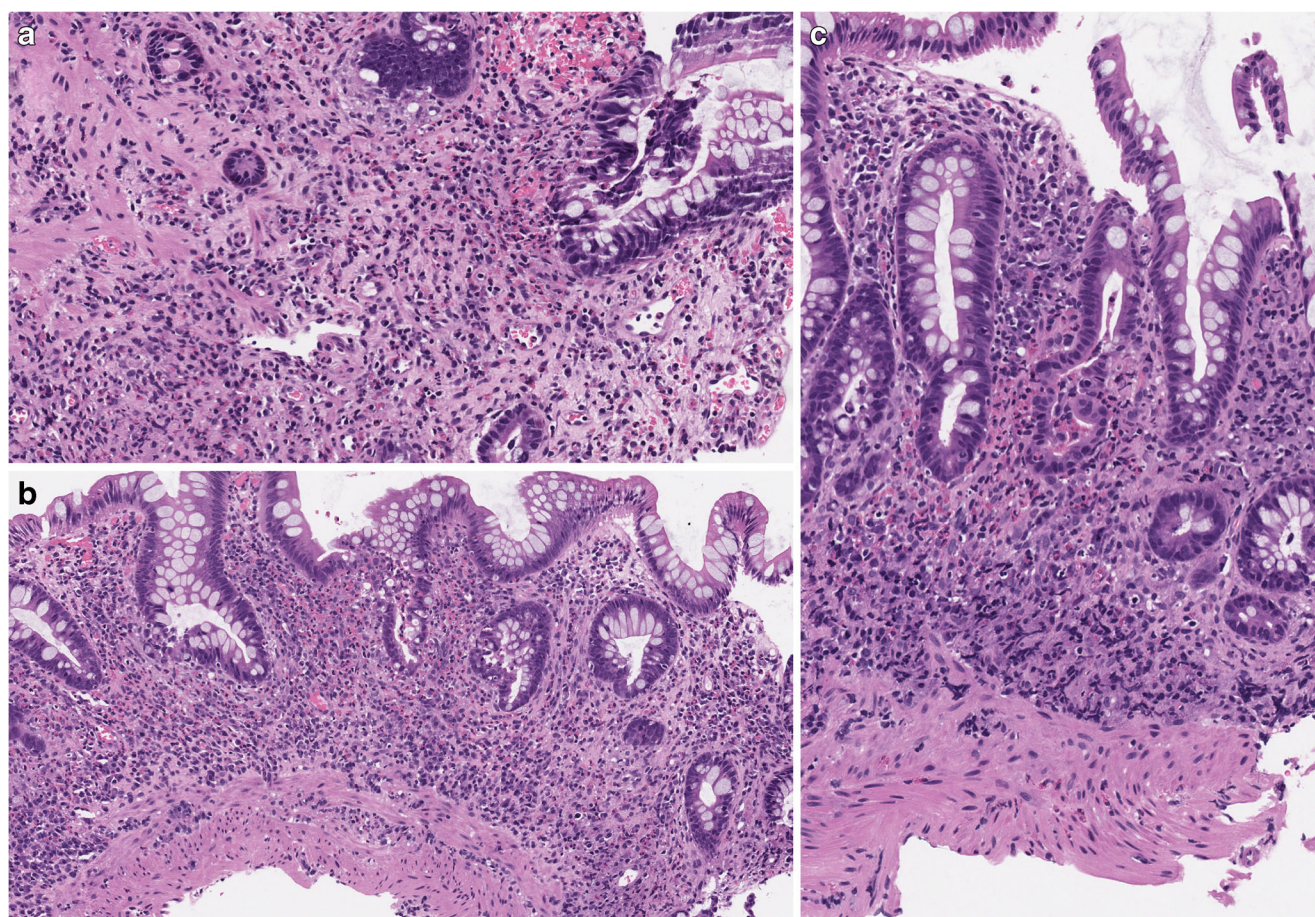


Fig. 2 Multiple colonic biopsies from the ascending colon (a) and transverse colon (b, c) showing a marked increase in the number of eosinophils in the lamina propria and an occasional eosinophilic crypt abscess (c)

Fig. 3 Biopsies from the sigmoid colon showing a marked increase in lamina propria eosinophils

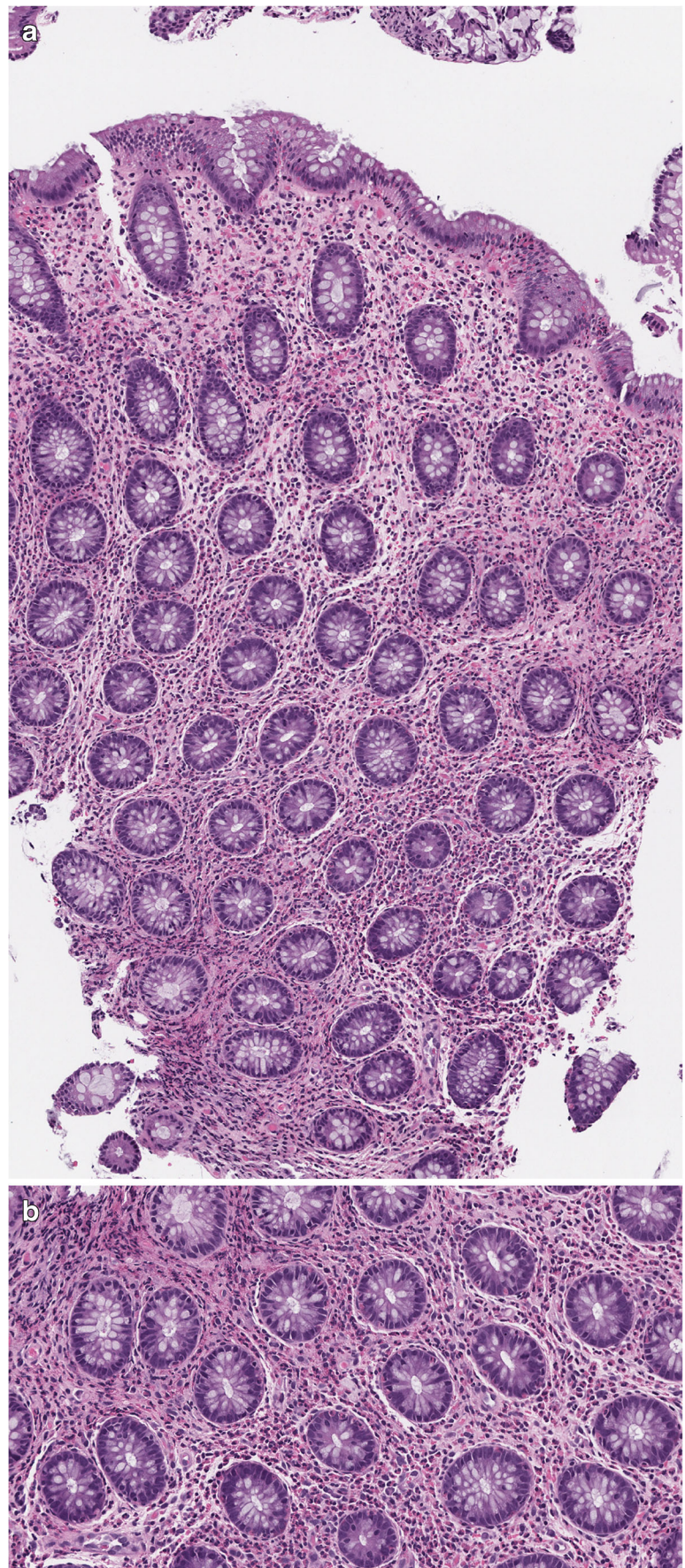


Table 3 Suggested minimum eosinophil count per HPF for a pathological diagnosis of eosinophilic colitis based on the site in the colon

Site in colon	Number of eosinophils/HPF
Right colon	> 50 eosinophils/HPF
Transverse colon	> 35 eosinophils/HPF
Left colon	> 25 eosinophils/HPF

Reference population: Texas, USA

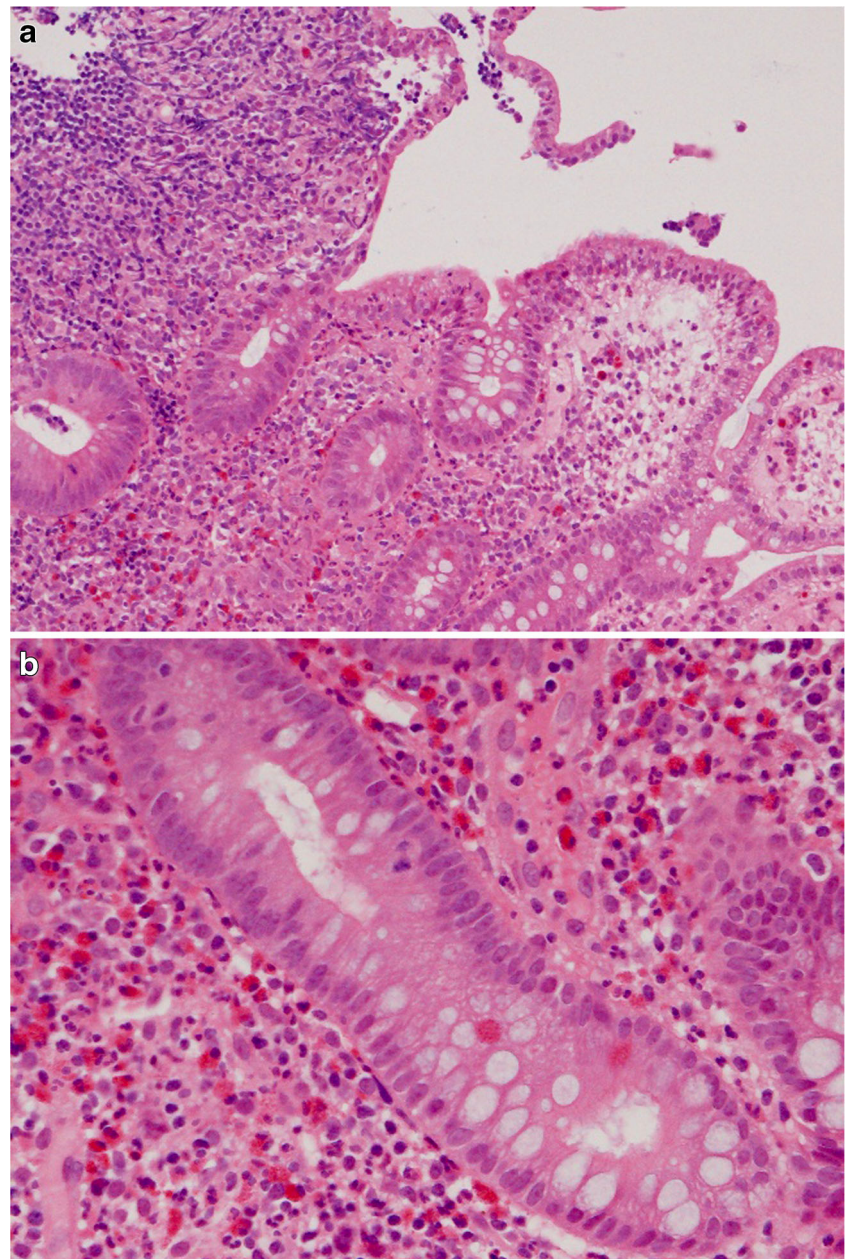
HPF high power field

tissue eosinophilia. Peripheral eosinophilia may or may not be present (the eosinophil count is normal in 25% of patients [33]).

Fig. 4 Terminal ileal biopsy from a middle-aged female with diarrhoea, weight loss and peripheral blood eosinophilia. Acute erosive ileitis with abundant eosinophils in the lamina propria is seen. This patient had a long history of asthma and autoimmune thyroiditis and likely has a primary allergic eosinophilic ileitis

Sixteen percent of patients with EGID have a family member with a similar disorder, indicating an interaction between genetic and environmental factors [32]. An allergic component is likely in EGIDs, as many patients (50–70%) have allergic histories (62% experience specific food sensitivities [34]), 80% have a co-existent atopic disease, and many have elevated serum IgE [32] (Fig. 4).

EGE and EC are best categorised into primary (idiopathic) or secondary EGE/EC. Secondary disorders associated with these two disorders are similar, and include the hypereosinophilic syndrome, coeliac disease, IBD, connective tissue disease (e.g. scleroderma, scleroderma variants, dermatomyositis, polymyositis [11], vasculitis (e.g. Churg–Strauss syndrome (Fig. 5), polyarteritis



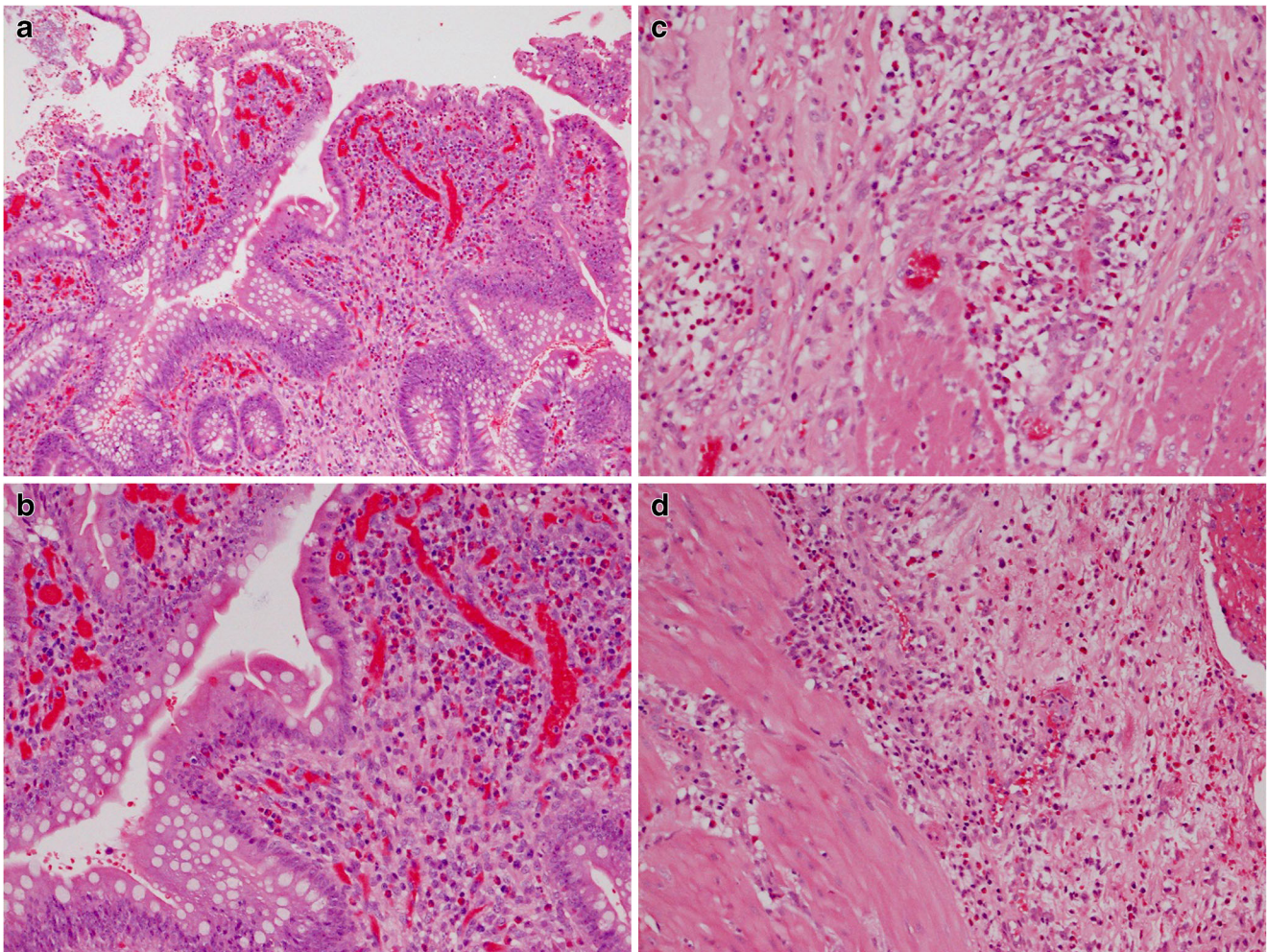


Fig. 5 Images from a diagnostic full thickness small bowel resection in a patient with intermittent peripheral blood eosinophilia and small bowel obstruction. Partial villous atrophy (a) with increased lamina propria eosinophils (b) is present. Deep submucosal perivascular granulomas

with numerous eosinophils (c) are seen. Extensive serosal eosinophilia (d) is also present. cANCA positivity confirmed a diagnosis of Churg–Strauss syndrome

nodosa), infection (e.g. *Helicobacter pylori*, parasites, fungi) and drug injury [9] (Table 4).

Eosinophilic gastroenteritis

EGE is an uncommon chronic disease [25]. The incidence has risen in recent years, probably due to increased interest and better recognition [25], with an estimated incidence of approximately 1/100,000 population. It can affect individuals of any age (peak incidence at 20–50 years of age) [11, 35]. Patients may report a history of allergy (e.g. asthma, rhinitis, drug allergy and/or eczema). Peripheral blood eosinophilia and elevated serum IgE are usually, but not always, present [24].

As mentioned previously, the disorder is best categorised into primary (idiopathic) or secondary EGE. The term primary EGE is applied to a diverse group of patients who share the following characteristics: (a) GI symptoms, (b) GI eosinophilic infiltrates, (c) no demonstrable cause of the eosinophilia

(e.g. parasitic infection or a specific allergic response) [33] (Table 5).

The commonest sites of involvement are the stomach and proximal small intestine [24, 32, 36]. Symptoms of EGE are dependent on the intensity and the location of eosinophils within the layers of the GIT [33]. Approximately 57% of patients have mucosal disease, 30% of patients have involvement of the muscle layer and 12.5% of patients have serosal/subserosal disease [33]. Patients with eosinophilic infiltration of the mucosa have non-specific symptoms and signs, similar to those of IBD, such as nausea, vomiting, diarrhoea, anaemia (due to chronic inflammation or iron deficiency), and/or clinical manifestations secondary to malabsorption. Infiltration of the muscularis propria by eosinophils leads to intestinal obstruction (most commonly jejunal obstruction) secondary to the thickening of intestinal wall [19, 37]. Clinical presentation of eosinophilic infiltration of the serosa is usually characterised by ascites, sometimes associated with symptoms

Table 4 Causes of eosinophilic enteritis and eosinophilic colitis

Primary EGID	- Genetic - Environmental - Allergic
Secondary causes of eosinophilic enteritis and eosinophilic colitis	- Coeliac disease - Inflammatory bowel disease – Crohn's disease, ulcerative colitis, pouchitis - Infections – parasitic and non-parasitic - Drugs - Collagenous and lymphocytic colitis - Hypereosinophilic syndrome - Graft-versus-host disease - Autoimmune colitis - Neoplastic lesions – inflammatory fibroid polyp, inflammatory myofibroblastic tumour, carcinoma, T cell lymphoma, eosinophilic leukinaemia - Radiation - Connective tissue disease and vasculitis - Deficiencies of magnesium, vitamin E and selenium - Toxic oil syndrome - Peritoneal dialysis - Hyperimmunoglobulinaemia E

Abbreviations: *EGID*, eosinophilic gastrointestinal disease

of intestinal obstruction. Ascitic fluid shows marked eosinophilia.

Diagnosis requires endoscopy and biopsy. The endoscopic appearance is non-specific, and endoscopy may show erythematous, friable, nodular or ulcerated mucosa [26].

The diagnosis on biopsy and resection specimens is made by observing a large number of eosinophils in the mucosa and submucosa, including oedema of the latter, if included. It is not sufficient to see elevated numbers of eosinophils; eosinophils have to be the dominant cell type, with little or no increase in other inflammatory cell types. As outlined previously, the most accepted definition of EGE is a count that exceeds 20 eosinophils/HPF in at least one sample [25–27] (Table 1). Crypt hyperplasia, epithelial cell necrosis, and villous atrophy may also be seen [24].

In resection specimens, the muscularis propria and subserosa can also be involved. In addition, an increase in

Table 5 Criteria for a diagnosis of primary eosinophilic gastroenteritis

Gastrointestinal symptoms
Gastrointestinal eosinophilic infiltrates
No demonstrable cause of the eosinophilia (e.g. parasitic infection, a specific allergic response, etc.)

mast cells is usually seen [8]. Signs of other inflammatory diseases are absent—there is no evidence of crypt architectural distortion, worms, eggs or larvae.

Eosinophilic colitis

EC is the least common entity within the group of primary EGIDs [38]. There has been a rise in cases over the last decade, possibly due to increased recognition of it as a distinct disease entity [32]. Although first described more than 60 years ago, EC has remained an obscure entity and there is no clear understanding of its clinical impact or natural history [38].

As outlined previously, EC can be primary or secondary [38]. Primary EC represents an inflammatory disorder in which eosinophils infiltrate the gut wall, in the absence of known causes [32, 38]. A colitis that is dominated by an eosinophilic infiltration may also occur secondarily, in association with atopic processes (typically in the infants and in young patients) [31, 39, 40], infections (such as with *Strongyloides stercoralis*, *Enterobius vermicularis*, *Trichuris trichiura* or *Ancylostoma* [41–44], IBD [45], drug-induced reactions [46–52], neoplasias, connective tissue diseases [53, 54], hypereosinophilic syndrome [55], diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome and eosinophilic myositis [16], amongst other causes [9] (Fig. 6). All of these secondary causes must be excluded before making a diagnosis of primary EC.

As with EGE, clinical presentation of EC depends on the location of eosinophils within the layers of the large bowel [38]. Infiltration of the mucosa by eosinophils tends to cause diarrhoea. Mucosa-predominant disorder is often associated with

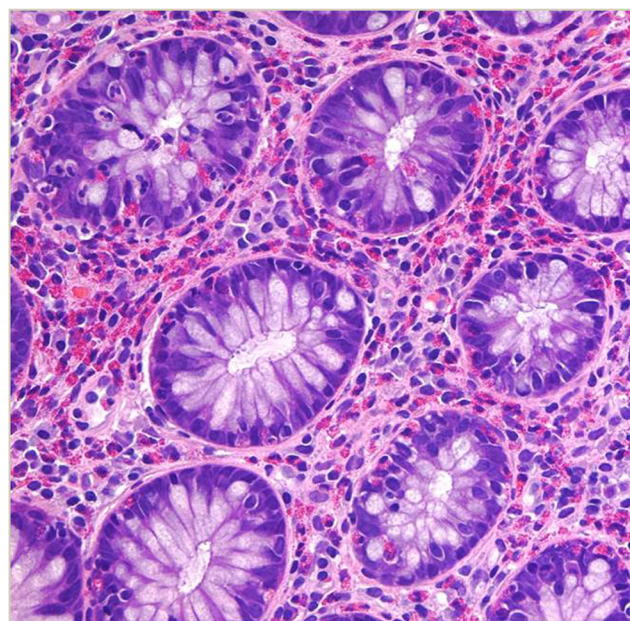


Fig. 6 Eosinophilic colitis. Almost 100% of the lamina propria cellularity is due to eosinophils. There is a wide differential diagnosis (see Table 4)

mucosal injury [32], although the overall architecture of the mucosa is typically well-preserved [11, 56]. Transmural eosinophilia is associated with colonic wall thickening and intestinal obstruction. Serosal eosinophilic infiltration is associated with eosinophilic ascites (up to 95% eosinophils in ascitic fluid) [38]. The right colon is involved more often than other parts of the large intestine [57].

Endoscopy may reveal oedematous mucosa with a loss of the normal vascular pattern, patchy erythematous changes, and/or superficial ulcerations.

In 2014, Alfadda and colleagues described seven patients with EC. Colonic biopsies from all patients showed a dense eosinophilic infiltrate (> 20 eosinophils/HPF) involving the lamina propria [27, 38]. They suggested making the diagnosis of primary eosinophilic colitis contingent on the presence of a dense eosinophilic infiltrate in one or more segments of the colon, without evidence of parasites or other underlying disease [32, 58].

Allergic proctocolitis in infants

In very young infants (nearly always younger than 1 year of age), allergic proctocolitis is a well-recognized entity and is among the commonest causes of diarrhoea and rectal bleeding in this age group [11]. It is related to intolerance to human or cows' milk protein or to soy protein in formula.

Endoscopic biopsies typically show infiltration of the mucosa by large numbers of eosinophils (> 60 eosinophils/10hpf) that can involve any colonic segment (but preferentially involves the rectosigmoid) [30, 59–61]. Typically, there are no other significant histological abnormalities. Severe cases may show superficial aphthous erosions or frank ulcerations covered by a surface exudate.

The condition resolves following exclusion of the offending protein. The prognosis is very good and triggering foods can be re-introduced by 1–3 years of age.

Allergy-associated colitis in adults

There is substantial evidence that allergic reactions similar to allergic proctocolitis in infants also exist in adults (aged 3rd–7th decade), which can be allergy-associated or due to drugs (e.g. non-steroidal anti-inflammatory drugs (NSAIDs)) [11]. Allergy-associated colitis in adults can affect the ileum as well as the colon and, but the rectum is typically uninvolved.

Patients with allergy-related colitis pose a diagnostic challenge to their physicians as the clinical features are variable and non-specific, occurring in other GI disorders, and specific diagnostic tools are missing.

Ileal and colonic biopsies from patients with allergy-associated colitis show prominent eosinophilic infiltration of the epithelium, lamina propria, and submucosa, with variable

degrees of degranulation. Neutrophils or mononuclear infiltrates are not significantly increased, and damage to the epithelium is not prominent [11].

A definitive diagnosis depends upon careful clinical examination and exclusion of several differential diagnoses.

Secondary causes of eosinophilic gastroenteritis/colitis

Coeliac disease

Coeliac disease is a malabsorption syndrome which affects children and adults. It results from a specific immunological hyperreactivity to gliadin in the diet (gluten and other prolamins), inducing gliadin-specific immunoreactive cells which damage the mucosa.

Duodenal biopsies show hypercellularity of the lamina propria, containing eosinophils, mast cells, lymphocytes, plasma cells, macrophages, and neutrophils.

Other histological changes (increased numbers of intraepithelial lymphocytes, villous blunting/flattening) are highly characteristic, and when present clearly indicate the diagnosis of coeliac disease to the pathologist, in the correct clinical setting [62].

Eosinophilia associated with inflammatory bowel disease

Eosinophils are one of the many inflammatory cells involved in the pathogenesis of IBD. The two most important roles that eosinophils play in IBD appear to be as pro-motility and pro-inflammatory agents, thus producing effects such as diarrhoea, inflammation, tissue destruction, and formation of fibrosis and strictures [8].

Villanacci and colleagues evaluated the presence of basal plasmacytosis and eosinophils in more than 100 routine untreated cases of colitides and demonstrated that 80% of patients with evidence of basal plasmacytosis intermingled with eosinophils in biopsies from at least three ileocolic segments were subsequently classified as IBD [63]. They therefore concluded that the finding of basal plasmacytosis, associated with the presence of eosinophils, in colonic endoscopic biopsies of naïve patients with “colitis” seems to be a strong histological clue toward the presence of an IBD.

Bass et al. demonstrated that initial biopsies in children with an eventual diagnosis of IBD (ulcerative colitis (UC) or Crohn's disease (CD)) in comparison to biopsies from children with functional abdominal pain have significantly greater frequency of eosinophilia in the rectosigmoid area, in addition to crypt distortion in the colon and inflammation in the stomach [64].

Crohn's disease

Inflammation in CD is characterised by a prominent mononuclear cell infiltrate consisting predominantly of lymphocytes and plasma cells. The lamina propria typically also contains a large number of mast cells and eosinophils [65]. In addition, localized histiocytic collections are typically surrounded by lymphocytes, plasma cells, and eosinophils. Increased numbers of eosinophils, plasma cells, lymphocytes, macrophages, mast cells, and neutrophils can also be seen in all layers of the bowel wall [11].

Xu and colleagues examined the roles of eosinophils and mast cells in CD and found that they may affect fibrosis by directly influencing intestinal fibroblast properties [66].

Ulcerative colitis

Colonic biopsies in active chronic UC typically demonstrate an intense infiltrate of lymphocytes and plasma cells in the lamina propria with glandular distortion. Mast cells are also often increased in numbers [67].

A dense eosinophilic infiltrate may initially be present in UC, mimicking EC and implicating a pathogenetic role for eosinophils in IBD [45]. Although Lampinen and colleagues showed that the number of activated eosinophils was higher in the quiescent phase of UC than in the active phase [68], several studies have shown significantly more severe eosinophilic infiltration of the lamina propria in active UC compared with long-standing inactive disease [15, 69].

Tanaka and colleagues suggested that five histological criteria can reliably predict failure of medical treatment in patients with UC, namely eosinophil infiltration, crypt abscess formation, mononuclear cell infiltration, ulceration and endoscopic disease extent [70, 71]. In particular, they found that infiltration of the lamina propria by eosinophils was significantly lower in patients with active UC not responding to medical treatment and ultimately requiring colectomy. In stark contrast, however, Zezos and others have shown that severe eosinophilic infiltration in patients with active UC was the most significant predictor of no response to medical treatment [15, 69].

It has been shown that focal eosinophilic mucosal infiltration is an important parameter in the histological differential diagnosis between colonic CD and UC, with CD demonstrating a significantly higher mean percentage of eosinophils in areas with focal inflammation [72].

Infection-associated eosinophilia of the gastrointestinal mucosal

Parasitic infections (organisms such as schistosoma, strongyloides, ancylostoma) can effect patients of all ages [11].

A prominent or focal eosinophilic infiltrate in the lamina propria of the small bowel or large bowel and mural oedema is seen in patients with helminthic infections. Increased numbers of lamina propria eosinophils are particularly prominent near areas of parasitic attachment.

Helminth larvae, worms or eggs may not always be seen in histological sections, and so it is important for pathologists to be aware of any relevant history of travel and the endoscopic findings. If parasitic aetiology is suspected, stool examination or specific serology may be performed [56].

Patients may also exhibit regional lymphadenopathy due to the presence of granulomata with central eosinophilic degranulation and degradation products.

Infectious non-parasitic and bacteria-associated inflammatory diseases can also be associated with non-specific increased numbers of eosinophils as a sequel of acute inflammation (Table 6).

Drug-induced eosinophilia of the gastrointestinal mucosa

Colonic eosinophilic infiltration can occur secondarily to drugs, such as NSAIDs (e.g. naproxen) [46, 52], clozapine [32], carbamazepine [73], azathioprine, rifampicin and gold [7, 49, 74]. Liver transplant recipients maintained on tacrolimus as an immunosuppressive agent, are at risk of developing colonic eosinophilia; symptomatic improvement occurs when the immunosuppression is reduced [47]. The density of eosinophils in the colon can also increase following radiotherapy treatment (Table 7).

Hypereosinophilic syndrome:

Hypereosinophilic syndrome (HES) is a heterogeneous group of rare systemic diseases of idiopathic origin, characterized by marked blood eosinophilia (at least 1500 cells/mm³) persisting for more than 6 months. HES predominantly affects males, aged between 20 and 50 years [75, 76]. HES patients traditionally develop eosinophilic endocardial disease with embolization of peripheral organs (e.g. extremities, brain, skin, heart, lungs) [31, 78]. Serum contains high levels of mast cell tryptase [77] and bone marrow analyzes show a high number of dysplastic mast cells which typically decrease after treatment with the tyrosine kinase inhibitor imatinib mesylate [78] (Table 8). Consequently, it is thought that HES could be related to systemic mastocytosis and chronic myelogenous leukemia.

Table 6 Infections associated with eosinophilic gastrointestinal diseases

Parasites, e.g. <i>Strongyloides stercoralis</i> , <i>Enterobius vermicularis</i> , <i>Trichuris trichiura</i> or <i>Ancylostoma</i>
Bacteria, e.g. <i>Helicobacter pylori</i>

Table 7 Drugs associated with eosinophilic colitis

NSAIDs, e.g. naproxen
Mycophenolate
Azathioprine
Rifampicin
Clozapine
Carbamazepine
Gold
Tacrolimus

NSAIDs non-steroidal anti-inflammatory drugs

Thus, as per the definition, patients with EGIDs (typically EGE) and sustained blood eosinophilia exceeding 1500 cells/mm³ would be considered to have HES. Therefore, routine surveillance of the cardio-respiratory system is warranted, especially if the patients have extra-GI manifestations.

Eosinophilia associated with connective tissue disease

Connective tissue disease, particularly scleroderma (also dermatomyositis, polymyositis), has been reported to be associated with episodic peripheral eosinophilia and a band-like mast cell-rich eosinophilic infiltrate in the lamina propria of the large bowel [79]. One study by Clouse and colleagues described the presence of a peri-cryptal eosinophilic infiltrate in the colon, in patients with chronic diarrhoea and systemic connective tissue disease [80].

Vasculitis

In polyarteritis nodosa and Churg–Strauss syndrome, vasculitis is characterized by an infiltrate of eosinophils involving the small blood vessels in the GIT and in extra-intestinal organs (e.g. skin, lung, kidney, nervous system) [81].

Peripheral eosinophilia, along with elevated markers of inflammation and autoantibodies are typically present.

Collagenous and lymphocytic colitis

Some patients with chronic watery non-bloody idiopathic diarrhoea have histological evidence of colitis (microscopic colitis), even though the endoscopic appearance of the bowel is normal.

Table 8 Features of hypereosinophilic syndrome

Marked blood eosinophilia (at least 1500 cells/mm ³) persisting for more than 6 months
Eosinophilic endocardial disease with embolization of peripheral organs (e.g. extremities, brain, skin, heart, lungs)
High levels of mast cell tryptase in serum
± Eosinophilic gastrointestinal disease

In collagenous colitis, the lamina propria focally contains slightly to moderately increased numbers of lymphocytes, plasma cells, and mast cells, admixed with variable numbers of eosinophils and neutrophils. Eosinophils can be focally prominent and, in rare cases, a diffuse increase in eosinophils can be seen [82].

In lymphocytic colitis, the lamina propria contains increased numbers of eosinophils, lymphocytes, and/or neutrophils [83]. Infiltration of the surface epithelium with eosinophils and neutrophils may also be seen [84].

Eosinophilia associated with neoplasia

Massive tumoural eosinophilia has been observed histologically in association with gastric and colonic adenocarcinomas [11]. Dense colonic eosinophilia is frequent in mastocytic colitis, either primary or part of systemic mastocytosis [16]. In fact, the neoplastic mast cells may even be masked by the dense eosinophilic infiltrate, requiring the pathologist to have a high index of suspicion. As mentioned previously, mild to moderate eosinophilia can also be seen in cancer tissues, following radiation therapy.

Eosinophilia associated with graft-versus-host disease

Graft-versus-host disease (GVHD) occurs when immunologically competent donor lymphoid cells (which bear different histocompatibility antigens) from the host are placed into an immunosuppressed recipient (usually in the setting of a bone marrow transplant).

The colon and rectum are often involved. Mucosal biopsies typically reveal focal acute colitis/proctitis with isolated crypt injury, apoptosis, and eosinophilic and neutrophilic infiltrates [11].

Eosinophils in the appendix and gallbladder

In surgical resection specimens from patients with appendicitis and cholecystitis, eosinophils are commonly observed, particularly when there has been a slight delay between the onset of symptoms and surgery [2]. Approximately 40% of appendices removed within 12–84 h of symptom onset display mural eosinophils, often in combination with lymphocytes [85]. Similarly, more than 20% of resected gallbladders contain numerous eosinophils in addition to other types of inflammatory cells [86]. It is thought that these findings reflect the ‘subacute’ phase of the inflammatory process, rather than a primary eosinophilic disorder, especially if eosinophils are not the major component of the infiltrate and are evenly dispersed among other inflammatory cells [2].

Treatment

Some patients have symptoms just for a short period of time and may need no treatment or just short-term treatment. The natural history of this disorder has not been well studied. In addition, the rarity of EGE and EC has limited any large prospective randomised therapeutic trials [9], and therefore there is no standard therapy [87]. Steroids are frequently used as the first line of treatment, along with dietary restriction [27]. However, many patients relapse with steroid withdrawal, so steroid-sparing agents can also be used.

Yan and colleagues proposed the following management plan for patients with symptomatic EC: (a) if possible, stop the intake of a drug related to EC; (b) treat parasites if present (even if IBD co-exists); (c) treat with mesalazine (an aminosalicylate); if mesalazine fails, montelukast (a leukotriene receptor antagonist) can be used [88]; if IBD co-exists with an eosinophilic infiltration of the colonic mucosa, treatment of IBD is indicated [39].

Newer biologic medications (e.g. anti-IL5 and anti-IgE therapies) targeting specific points along the inflammatory cascade are currently under investigation and may offer possible treatment options in these patients [87, 89, 90].

Conclusion

Eosinophils are normally scanty in the gastrointestinal tract, and increasing numbers of eosinophils can denote pathology. There are currently no consensus criteria or specific eosinophil counts to confirm the diagnosis of eosinophilic gastroenteritis or eosinophilic colitis. Thus, pathologists need to familiarize themselves with the eosinophil content of the different segments of the normal colon and regularly report cases with unequivocal increases of eosinophils. When eosinophilia is present histologically, a final diagnosis depends upon careful clinical correlation and exclusion of several differential diagnoses.

Most of the knowledge relating to gastrointestinal eosinophilic disorders has been acquired from isolated case reports of different ages, which makes it difficult to draw firm conclusions and reach a consensus to establish diagnostic criteria. Thus, further detailed clinical and morphological studies are necessary to determine exact diagnostic criteria, including cut-off values of eosinophils in normal and pathological gastrointestinal specimens.

Acknowledgements The authors thank Professor Runjan Chetty and Dr. Stefano Serra, Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto, Ontario, Canada for providing some images for this paper.

Compliance with ethical standards The authors have complied with ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

References

- Conner JR, Kirsch R (2017) The pathology and causes of tissue eosinophilia in the gastrointestinal tract. *Histopathology* 71(2):177–199
- Yantiss RK (2015) Eosinophils in the GI tract: how many is too many and what do they mean? *Mod Pathol* 28(Suppl 1):S7–21
- Lucendo AJ (2010) Eosinophilic diseases of the gastrointestinal tract. *Scand J Gastroenterol* 45(9):1013–1021
- Ronkainen J, Talley NJ, Aro P, Storskrubb T, Johansson SE, Lind T et al (2007) Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 56(5):615–620
- Cherian S, Smith NM, Forbes DA (2006) Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 91(12):1000–1004
- Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E et al (2005) Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 3(12):1198–1206
- Oh HE, Chetty R (2008) Eosinophilic gastroenteritis: a review. *J Gastroenterol* 43(10):741–750
- Al-Haddad S, Riddell RH (2005) The role of eosinophils in inflammatory bowel disease. *Gut* 54(12):1674–1675
- Yan BM, Shaffer EA (2009) Primary eosinophilic disorders of the gastrointestinal tract. *Gut* 58(5):721–732
- Behm CA, Ovington KS (2000) The role of eosinophils in parasitic helminth infections: insights from genetically modified mice. *Parasitol Today* 16(5):202–209
- Mueller S (2008) Classification of eosinophilic gastrointestinal diseases. *Best Pract Res Clin Gastroenterol* 22(3):425–440
- Kato M, Kephart GM, Talley NJ, Wagner JM, Sarr MG, Bonno M et al (1998) Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec* 252(3):418–425
- Mueller S, Aigner T, Neureiter D, Stolte M (2006) Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol* 59(11):1175–1180
- Schwab D, Müller S, Aigner T, Neureiter D, Kirchner T, Hahn EG et al (2003) Functional and morphologic characterization of eosinophils in the lower intestinal mucosa of patients with food allergy. *Eosinophils in Food Allergy. Am J Gastroenterol* 98:1525–1534
- Jeziorska M, Haboubi N, Schofield P, Woolley DE (2001) Distribution and activation of eosinophils in inflammatory bowel disease using an improved immunohistochemical technique. *J Pathol* 194(4):484–492
- Turner KO, Sinkre RA, Neumann WL, Genta RM (2017) Primary colonic eosinophilia and eosinophilic colitis in adults. *Am J Surg Pathol* 41(2):225–233
- Saad AG (2011) Normal quantity and distribution of mast cells and eosinophils in the pediatric colon. *Pediatr Dev Pathol* 14(4):294–300
- Polydorides AD, Banner BF, Hannaway PJ, Yantiss RK (2008) Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils. *Hum Pathol* 39(6):832–836
- DeBrosse CW, Case JW, Putnam PE, Collins MH, Rothenberg ME (2006) Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 9(3):210–218
- Lowichik A, Weinberg AG (1996) A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. *Mod Pathol* 9(2):110–114

21. Matsushita T, Maruyama R, Ishikawa N, Harada Y, Araki A, Chen D et al (2015) The number and distribution of eosinophils in the adult human gastrointestinal tract: a study and comparison of racial and environmental factors. *Am J Surg Pathol* 39(4):521–527
22. Pascal RR, Gramlich TL, Parker KM, Gansler TS (1997) Geographic variations in eosinophil concentration in normal colonic mucosa. *Mod Pathol* 10(4):363–365
23. Aceves S, Hirano I, Furuta GT, Collins MH (2012) Eosinophilic gastrointestinal diseases—clinically diverse and histopathologically confounding. *Semin Immunopathol* 34(5):715–731
24. Ingle SB, Hinge Ingle CR (2013) Eosinophilic gastroenteritis: an unusual type of gastroenteritis. *World J Gastroenterol* 19(31):5061–5066
25. Uppal V, Kreiger P, Kutsch E (2016) Eosinophilic gastroenteritis and colitis: a comprehensive review. *Clin Rev Allergy Immunol* 50(2):175–188
26. Chen MJ, Chu CH, Lin SC, Shih SC, Wang TE (2003) Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol* 9(12):2813–2816
27. Lee CM, Changchien CS, Chen PC, Lin DY, Sheen IS, Wang CS et al (1993) Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 88(1):70–74
28. Talley NJ, Walker MM, Aro P, Ronkainen J, Storskrubb T, Hindley LA et al (2007) Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. *Clin Gastroenterol Hepatol* 5(10):1175–1183
29. Gonsalves N (2007) Food allergies and eosinophilic gastrointestinal illness. *Gastroenterol Clin N Am* 36(1):75–91
30. Odze RD, Bines J, Leichtner AM, Goldman H, Antonioli DA (1993) Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. *Hum Pathol* 24(6):668–674
31. Rothenberg ME (2004) Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 113(1):11–28
32. Alfadda AA, Storr MA, Shaffer EA (2011) Eosinophilic colitis: epidemiology, clinical features, and current management. *Therap Adv Gastroenterol* 4(5):301–309
33. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR (1990) Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 31(1):54–58
34. Guajardo JR, Plotnick LM, Fende JM, Collins MH, Putnam PE, Rothenberg ME (2002) Eosinophil-associated gastrointestinal disorders: a world-wide-web based registry. *J Pediatr* 141(4):576–581
35. Cianferoni A, Spergel JM (2015) Eosinophilic esophagitis and gastroenteritis. *Curr Allergy Asthma Rep* 15(9):58
36. Khan S, Orenstein SR (2002) Eosinophilic gastroenteritis: epidemiology, diagnosis and management. *Paediatr Drugs* 4(9):563–570
37. Yun MY, Cho YU, Park IS, Choi SK, Kim SJ, Shin SH et al (2007) Eosinophilic gastroenteritis presenting as small bowel obstruction: a case report and review of the literature. *World J Gastroenterol* 13(11):1758–1760
38. Alfadda AA, Shaffer EA, Urbanski SJ, Storr MA (2014) Eosinophilic colitis is a sporadic self-limited disease of middle-aged people: a population-based study. *Color Dis* 16(2):123–129
39. Fernández Salazar L, Borrego Pintado H, Velayos Jiménez B, González Hernández JM (2013) Differential diagnosis and management of histologic eosinophilic colitis. *J Crohns Colitis* 7(1):e20–e21
40. Inamura H, Kashiwase Y, Morioka J, Suzuki K, Igarashi Y, Kurosawa M (2006) Accumulation of mast cells in the interstitium of eosinophilic colitis. *Allergol Immunopathol (Madr)* 34(5):228–230
41. Minematsu H, Hokama A, Makishi T, Arakaki K, Kinjo F, Fujita J (2011) Colonoscopic findings and pathologic characteristics of Strongyloides colitis: a case series. *Digestion* 83(3):210–214
42. Tsibouris P, Galeas T, Moussia M, Sotiropoulou M, Michopoulos S, Kralios N (2005) Two cases of eosinophilic gastroenteritis and malabsorption due to Enterobius vermicularis. *Dig Dis Sci* 50(12):2389–2392
43. Hong ST, Lim HS, Kim DH, Kim SJ (2003) A case of gastroenteritis associated with gastric trichuriasis. *J Korean Med Sci* 18(3):429–432
44. Walker NI, Croese J, Clouston AD, Parry M, Loukas A, Prociw P (1995) Eosinophilic enteritis in northeastern Australia. Pathology, association with Ancylostoma caninum, and implications. *Am J Surg Pathol* 19(3):328–337
45. Uzunismail H, Hatemi I, Doğusoy G, Akin O (2006) Dense eosinophilic infiltration of the mucosa preceding ulcerative colitis and mimicking eosinophilic colitis: report of two cases. *Turk J Gastroenterol* 17(1):53–57
46. Jiménez-Sáenz M, González-Cámpora R, Linares-Santiago E, Herrerías-Gutiérrez JM (2006) Bleeding colonic ulcer and eosinophilic colitis: a rare complication of nonsteroidal anti-inflammatory drugs. *J Clin Gastroenterol* 40:84–85
47. Saeed SA, Integlia MJ, Pleskow RG, Calenda KA, Rohrer RJ, Dayal Y et al (2006) Tacrolimus-associated eosinophilic gastroenterocolitis in pediatric liver transplant recipients: role of potential food allergies in pathogenesis. *Pediatr Transplant* 10(6):730–735
48. Friedberg JW, Frankenburg FR, Burk J, Johnson W (1995) Clozapine-caused eosinophilic colitis. *Ann Clin Psychiatry* 7(2):97–98
49. Lange P, Oun H, Fuller S, Turney JH (1994) Eosinophilic colitis due to rifampicin. *Lancet* 344(8932):1296–1297
50. Anttila VJ, Valtonen M (1992) Carbamazepine-induced eosinophilic colitis. *Epilepsia* 33(1):119–121
51. Jiménez-Sáenz M (2006) Naproxen: bleeding colonic ulcer, eosinophilic colitis. *Clin-Alert* 44(2):1–8
52. Bridges AJ, Marshall JB, Diaz-Arias AA (1990) Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med* 89(4):526–527
53. Ahmad M, Soetikno RM, Ahmed A (2000) The differential diagnosis of eosinophilic esophagitis. *J Clin Gastroenterol* 30(3):242–244
54. Barbie DA, Mangi AA, Lauwers GY (2004) Eosinophilic gastroenteritis associated with systemic lupus erythematosus. *J Clin Gastroenterol* 38(10):883–886
55. Roufosse FE, Goldman M, Cogan E (2007) Hypereosinophilic syndromes. *Orphanet J Rare Dis*
56. Bates WH (2012) Diagnosing eosinophilic colitis: histopathological pattern or nosological entity? *Scientifica (Cairo)*. <https://doi.org/10.6064/2012/682576>
57. Naylor AR, Pollet JE (1985) Eosinophilic colitis. *Dis Colon rectum* 28(8):615–618
58. Alfadda AA, Storr MA, Shaffer EA (2011) Eosinophilic colitis: an update on pathophysiology and treatment. *Br Med Bull* 100:59–72
59. Winter HS, Antonioli DA, Fukagawa N, Marcial M, Goldman H (1990) Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol* 3(1):5–10
60. Odze RD, Wershil BK, Leichtner AM, Antonioli DA (1995) Allergic colitis in infants. *J Pediatr* 126(2):163–170
61. Goldman H, Proujansky R (1986) Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. *Am J Surg Pathol* 10(2):75–86
62. Brown IS, Smith J, Rosty C (2012) Gastrointestinal pathology in celiac disease: a case series of 150 consecutive newly diagnosed patients. *Am J Clin Pathol* 138(1):42–49
63. Villanacci V, Antonelli E, Reboldi G, Salemm M, Casella G, Bassotti G (2014) Endoscopic biopsy samples of naïve “colitides” patients: role of basal plasmacytosis. *J Crohns Colitis* 8(11):1438–1443

64. Bass JA, Friesen CA, Deacy AD, Neilan NA, Bracken JM, Shakhnovich V, et al (2015) Investigation of potential early histologic markers of pediatric inflammatory bowel disease. *BMC Gastroenterol*. <https://doi.org/10.1186/s12876-015-0359-2>
65. Carvalho AT, Elia CC, de Souza HS, Elias PR, Pontes EL, Lukashok HP et al (2003) Immunohistochemical study of intestinal eosinophils in inflammatory bowel disease. *J Clin Gastroenterol* 36(2):120–125
66. Xu X, Rivkind A, Pikarsky A, Pappo O, Bischoff SC, Levi-Schaffer F (2004) Mast cells and eosinophils have a potential profibrogenic role in Crohn disease. *Scand J Gastroenterol* 39(5):440–447
67. Nolte H, Spjeldnaes N, Kruse A, Windelborg B (1990) Histamine release from gut mast cells from patients with inflammatory bowel diseases. *Gut* 31(7):791–794
68. Lampinen M, Rönblom A, Amin K, Kristjansson G, Rorsman F, Sangfelt P et al (2005) Eosinophil granulocytes are activated during the remission phase of ulcerative colitis. *Gut* 54(12):1714–1720
69. Zezos P, Patsiaoura K, Nakos A, Mpoumponaris A, Vassiliadis T, Giouleme O et al (2014) Severe eosinophilic infiltration in colonic biopsies predicts patients with ulcerative colitis not responding to medical therapy. *Color Dis* 16(12):420–430
70. Tanaka M, Kusumi T, Oshitani N, Nishigami T, Iwao Y, Hatada Y et al (2003) Validity of simple mucosal biopsy criteria combined with endoscopy predicting patients with ulcerative colitis ultimately requiring surgery: a multicenter study. *Scand J Gastroenterol* 38(6):594–598
71. Tanaka M, Saito H, Kusumi T, Shimoyama T, Fukuda S, Morita T et al (2002) Biopsy pathology predicts patients with ulcerative colitis subsequently requiring surgery. *Scand J Gastroenterol* 37(2):200–205
72. Rubio CA (2003) A method for the detection of eosinophilic granulocytes in colonoscopic biopsies from IBD patients. *Pathol Res Pract* 199(3):145–150
73. Velchuru VR, Khan MA, Hellquist HB, Studley JG (2007) Eosinophilic colitis. *J Gastrointest Surg* 11(10):1373–1375
74. Martin DM, Goldman JA, Gilliam J, Nasrallah SM (1981) Gold-induced eosinophilic enterocolitis: response to oral cromolyn sodium. *Gastroenterology* 80(6):1567–1570
75. Straumann A (2008) Idiopathic eosinophilic gastrointestinal diseases in adults. *Best Pract Res Clin Gastroenterol* 22(3):481–496
76. Weller PF, Bubley GJ (1994) The idiopathic hypereosinophilic syndrome. *Blood* 83(10):2759–2779
77. Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J et al (2003) Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 101(12):4660–4666
78. Klion AD, Robyn J, Akin C, Noel P, Brown M, Law M et al (2004) Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 103(2):473–478
79. DeSchryver-Kecskemeti K, Clouse RE (1984) A previously unrecognized subgroup of “eosinophilic gastroenteritis”. Association with connective tissue diseases. *Am J Surg Pathol* 8(3):171–180
80. Clouse RE, Alpers DH, Hockenbery DM, DeSchryver-Kecskemeti K (1992) Pericrypt eosinophilic enterocolitis and chronic diarrhea. *Gastroenterology* 103(1):168–176
81. Solans R, Bosch JA, Pérez-Bocanegra C, Selva A, Huguet P, Alijotas J et al (2001) Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. *Rheumatology (Oxford)* 40(7):763–771
82. Weidenhiller M, Müller S, Schwab D, Hahn EG, Raithel M, Winterkamp S (2005) Microscopic (collagenous and lymphocytic) colitis triggered by food allergy. *Gut* 54(2):312–313
83. Mills LR, Schuman BM, Thompson WO (1993) Lymphocytic colitis. A definable clinical and histological diagnosis. *Dig Dis Sci* 38(6):1147–1151
84. Bo-Linn GW, Vendrell DD, Lee E, Fordtran JS (1985) An evaluation of the significance of microscopic colitis in patients with chronic diarrhea. *J Clin Invest* 75(5):1559–1569
85. Ciani S, Chuaqui B (2000) Histological features of resolving acute, non-complicated phlegmonous appendicitis. *Pathol Res Pract* 196(2):89–93
86. Dabbs DJ (1993) Eosinophilic and lymphoeosinophilic cholecystitis. *Am J Surg Pathol* 17(5):497–501
87. Jawairia M, Shahzad G, Mustacchia P (2012) Eosinophilic gastrointestinal diseases: review and update. *ISRN Gastroenterol*. <https://doi.org/10.5402/2012/463689>
88. De Maeyer N, Kochuyt AM, Van Moerkercke W, Hiele M. Montelukast as a treatment modality for eosinophilic gastroenteritis. *Acta Gastroenterol Belg* 2011;74(4):570–575
89. Stein ML, Villanueva JM, Buckmeier BK, Yamada Y, Filipovich AH, Assa'ad AH et al (2008) Anti-IL-5 (mepolizumab) therapy reduces eosinophil activation ex vivo and increases IL-5 and IL-5 receptor levels. *J Allergy Clin Immunol* 121(6):1473–1483
90. Foroughi S, Foster B, Kim N, Bernardino LB, Scott LM, Hamilton RG et al (2007) Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol* 120(3):594–601