PATHOLOGICA 2022;114:79-88;
DOI: 10.32074/1591-951X-734

Review

Pathologist's approach to paediatric and neonatal eosinophilic gastrointestinal disorders

Michela Campora[1]*, Luca Mastracci[2-3]*, Luca Carlin[3], Elettra Unti[4], Paola Parente[5], Matteo Fassan[6-7], Jacopo Ferro[3], Maria Elena Errico[8], Vittoria Donofrio[8], Federica Grillo[2-3]

** These authors contributed equally*

[1] Anatomic Pathology, Ospedale Santa Chiara, Trento, Italy; [2] Anatomic Pathology, Ospedale Policlinico San Martino IRCCS, Genova, Italy; [3] Anatomic Pathology, Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genova, Genova, Italy; [4] Unit of Pathology, Civico-Di Cristina-Benfratelli Hospitals, Palermo, Italy; [5] Unit of Pathology, Fondazione IRCCS Casa Sollievo della Sofferenza, Viale Cappuccini 1, 71013 San Giovanni Rotondo, FG, Italy; [6] Department of Medicine (DIMED), Surgical Pathology & Cytopathology Unit, University of Padua, Padua, Italy; [7] Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [8] Anatomia Patologica, Unit of Pathology, AORN Santobono Pausilipon, Ospedale Pausilipon, Naples, Italy

Summary

Children are not simply miniature adults. The evaluation of their gastrointestinal disorders is therefore different from that in full-grown adults and requires a particular clinical/pathologic approach.

Different studies have tried to assess the normal eosinophil distribution in the gastrointestinal tract in adults while very few studies have investigated the paediatric population, consequently complicating the pathologist's ability in identifying an abnormal number of eosinophils in this setting of patients.

When evaluating gastrointestinal tract biopsies with eosinophilia, eosinophilic count must be considered along with other histological features like eosinophil distribution in the gastrointestinal wall, their degranulation, cryptitis and crypt abscesses, other accompanying inflammatory cells, apoptotic bodies, foreign material or microorganisms; these findings, although rarely specific, may be a useful aid for diagnosis.

Reports should not include a diagnosis of primary eosinophilic gastrointestinal disorders (EoGID) if clinical data and test results do not rule out other forms of gastrointestinal eosinophilia. A more descriptive definition like "with eosinophilic pattern" should be favoured over a specific diagnosis of "eosinophilic disorder" in order to avoid potential confusion between different entities.

Key words: eosinophils, gastrointestinal disorders, paediatric and neonatal pathology

Received and accepted: December 23, 2021

Correspondence
Donofrio Vittoria
Anatomia Patologica, Unit of Pathology,
AORN Santobono Pausilipon, Ospedale Pausilipon, via Posillipo 226, 80122 Naples, Italy
Tel.: +39 081 2205586
Fax: +39 081 2205546
E-mail: vittoriadono@gmail.com

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Campora M, Mastracci L, Carlin L, et al. Pathologist's approach to paediatric and neonatal eosinophilic gastrointestinal disorders. Pathologica 2022;114:79-88. https://doi.org/10.32074/1591-951X-734

Introduction

Children are not simply miniature adults. The evaluation of their gastrointestinal disorders is, therefore, different from that used in full-grown adults and requires a particular clinical/pathologic approach. Focusing on eosinophilic gastrointestinal disorders (EoGIDs), histology is characterised by increased number of mucosal eosinophils in the gastrointestinal (GI) tract. EoGIDs can be subclassified according to the affected site(s) as: eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EoGE) and eosinophilic colitis (EoC) [1]. Multiple sites can be interested simultaneously: the most frequent combination of multisite inflammation is the oesophagus and stomach/small intestine, followed by the oesophagus and stomach alone [2].

Different studies have tried to assess a range of normal eosinophil distribution in the GI tract in adults [3] while very few studies investigate distribution in the paediatric population [4,5], consequently complicating the pathologist's ability in identifying an abnormal number of eosinophils. Consensus recommendations for the diagnosis of EoGIDs are limited only to EoE, with some differences depending on the patients' age [6]. EoGIDs lead to organ dysfunction and clinical symptoms dependent on the site and extent (and layer) of involvement. They are considered immune-mediated chronic inflammatory disorders and find strong correlations with food allergen triggers [7]. Remedy strategies focus on either medical, dietary and/or behavioural therapies [5] but there is no consensus on the ideal treatment regimen. The aim of this report is to review the current literature providing guidelines for the pathologic diagnosis of the various forms of EoGID in paediatric and neonatal patients.

Normal distribution of eosinophils in the gastrointestinal tract

The eosinophil count varies considerably depending on the segment of gastrointestinal tract examined. Despite the increasing number of eosinophil-related pathologies in various organs, including the digestive system [8], the normal number and distribution of eosinophils, and subsequently their pathological increase, are still not well established.

With regards to the normal GI tract, published data concerning the adult population are almost aligned in describing a significant increase in the number of eosinophils from the esophagus to the duodenum, with a peak in number in the caecum and ascending colon, followed by a decrease proceeding to distal colonic segments and a final slight rise in the sigmoid tract. In a large study focusing on Japanese adult population [9] the mean eosinophil densities (± standard deviation) in the mucosa of the oesophagus, stomach, duodenum, terminal ileum, right colon and left segment-rectum were 0.07 ± 0.43/mm^2, 12.18 ± 11.39/mm^2, 33.51 ± 12.88/mm^2, 42.18 ± 35.28/mm^2, 36.59 ± 15.50/mm^2, and 8.53 ± 7.83/mm^2, respectively and similar ranges have been described in the Western adult population [10-12]. The studies present in the literature are often difficult to compare as eosinophil counts are expressed as wide ranges per High Power Field (HPF) with differing microscope field numbers instead of per mm^2.

In a large multicentric paediatric cohort of biopsies [4], the median peak eosinophil count/mm^2 and their interquartile ranges (in brackets) were: oesophagus 0 (0-0), stomach 10.2 (3.3-15.3), duodenum 56.1 (26.1-86.7), ileum 61.2 (49.0-91.8), cecum 76.5 (40.9-99.7), ascending colon 73.9 (49.5-131.4), transverse colon 66.3 (40.8-91.5), descending colon 66.3 (30.6-81.6), sigmoid colon 39.2 (27.8-51.0), rectum 25.5 (9.8-45.8), respectively. Saad [13] underlined that eosinophils were mainly observed within the lamina propria, and only rarely in the surface and crypt epithelium, such as in the cecum and the rectosigmoid tract, where they may be organised in small clusters.

Gastrointestinal Food Allergies (GIFA) are a heterogenous group of disorders, classified, according to their pathogenesis, as IgE-mediated food allergy (*Immediate hypersensitivity/anaphylaxis*), mixed IgE and non IgE-mediated disease (*primary EoGIDs*), and non IgE-mediated GIFA *(Food protein induced allergies)*. They share the immunologic reaction to specific dietary proteins and the recurrence of symptoms upon re-exposure. Food induced allergies include *food protein-induced enterocolitis syndrome* (FPIES), *food protein-induced enteropathies* (FPIE) and *food protein-induced allergic proctocolitis* (FPIAP); FPIES and FPIAP are the main cause of increase of the eosinophils in the gastrointestinal tract of very young patients.

Non IgE-mediated GIFAs have significantly increased worldwide in the last 20 years, particularly in westernised developed countries, with an estimated rate of prevalence of 2-7,5 % in otherwise healthy children [14]. They usually affect young children, the majority of whom are under 3 years of age [15].

Cow's milk – specifically whey protein (mainly B-lactoglobulin, but casein is also implicated) – is the most common food trigger in FPIES, FPE and FPIAP; the infant may be exposed to these antigens through breast milk or infant formula. Besides cow's milk, soy protein, wheat, egg and fish have been implicated in the development of GIFAs, and its treatment is based on the removal of these food antigens from the diet [16]. Symptoms may vary with a different gradient of severity, depending on the affected gut tract, and include persistent regurgitation, vomiting, chronic diarrhoea, rectal bleeding, feeding difficulties and unsettled behavior.

Food protein induced allergic proctocolitis (FPIAP), the most frequent GIFA, involves the distal colon, causing diarrhoea with mucus and bright rectal bleeding in infants. In addition to the increase of eosinophil number in the lamina propria, histologic examination reveals eosinophils in the glandular and surface epithelium and in the muscolaris mucosae; moreover, nodular lymphoid aggregates may be present (Fig. 1A).

Food Protein Induced Enteropathy (FPIE), predomi-

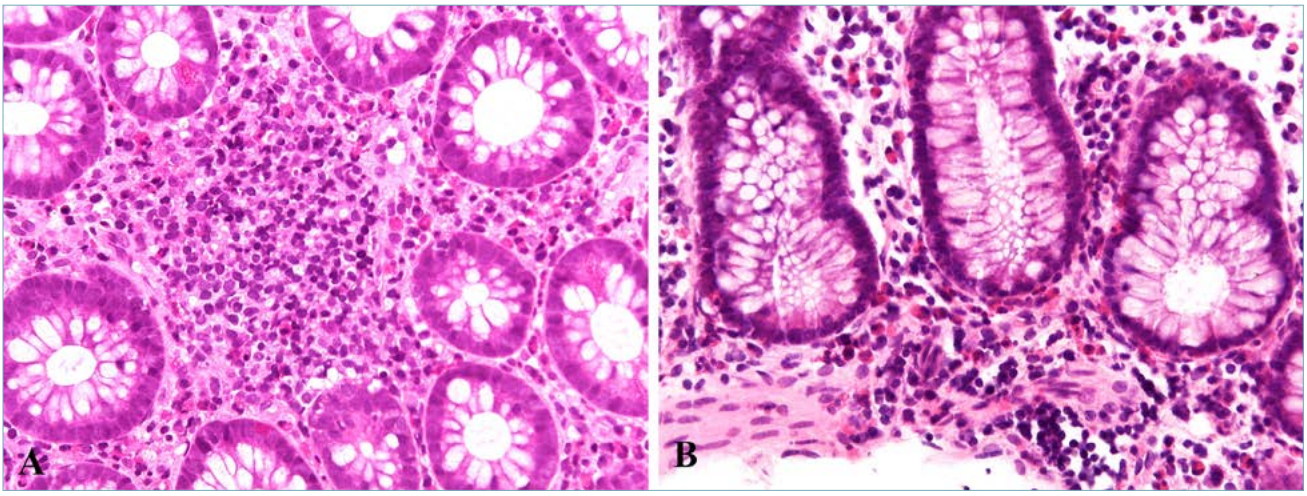

Figure 1. (A) Food protein induced allergic proctocolitis: presence of lymphoid aggregate and eosinophils in the lamina propria. H&E magnification 20x. (B) Chronic food protein-induced enterocolitis syndrome: besides eosinophils, plasma cells and scarce lymphocytes are present in the lamina propria. H&E magnification 40x.

nantly affects the small intestine, resulting in chronic diarrhea and malabsorption; the histologic findings of this entity are similar to those of celiac disease, but usually less severe and with variable degrees of jejunal villous atrophy and crypt hyperplasia.

Food protein-induced enterocolitis syndrome (FPIES), which may manifest acutely or chronically, can affect the entire gastrointestinal tract, predominantly causing symptoms of intractable vomiting, with dehydration and possible hypovolaemic shock in severe cases. They represent a spectrum of syndromes, that can overlap with primary EoGIDs at histology. Histologic findings vary from light infiltrate of lymphocytes and plasma cells to severe inflammation in the lamina propria, with an increased number of eosinophils, crypt abscesses and mucus depletion [17] (Fig. 1B).

The diagnosis of gastrointestinal food induced allergies requires a multidisciplinary approach, although it remains principally a clinical diagnosis. However, since the clinical presentation may be non-specific, and due to the lack of definitive diagnostic tests, the diagnostic workup may include endoscopy with biopsies in FPIE and in selected cases of FPIES and FPIAP [18].

Primary eosinophilic gastrointestinal disorders (EoGIDs) are considered the pathological result of an interplay between genetic predisposition, intestinal dysbiosis and environmental triggers. The prevalence of EoGIDs is increasing, apparently parallel with the incidence of allergic and immune-mediated disorders in Western countries [13]. Median age of EoGID presentation in children ranges from 6.5 to 8.1 years [2].

The most common presenting symptoms include failure to thrive in small children, reflux-like symptoms, vomiting, abdominal pain and food refusal in older children. Adolescents older than 13 have a similar clinical presentation to adults and usually present with dysphagia, solid food impaction and chest pain [19].

Pathological diagnosis of EoGIDs is impossible without accurate clinical correlation. The pathologist must be extremely careful when assessing digestive tract biopsies with an eosinophil-rich infiltrate, as this morphologic finding can be associated with many pathological conditions, from drugs to pinworms, gastrointestinal reflux disease and inflammatory bowel diseases, just to mention a few [20]. Lack of univocal and specific histologic features, make primary EoGIDs a diagnosis of exclusion, after all other causes of hyper-eosinophilia have been ruled out. The number of eosinophils alone does not yield any specific or reliable diagnostic clue: a detailed clinical history and examination followed by appropriate laboratory, radiology and endoscopic investigations are essential to allow the multidisciplinary team to make the correct diagnosis [21]. If all pertinent information is lacking, the term 'eosinophilic pattern' (e.g. "colitis with eosinophilic pattern"), together with an explanatory description of the morphologic findings, is preferable.

Despite the increasing prevalence of EoGIDs, uncertainty remains concerning the cut off in eosinophil number which reliably distinguishes healthy from pathologic specimens. With the exception of EoE, there is lack of consensus regarding the precise cut-off values, and this is especially true for the paediatric population. To complicate the situation even further,

the normal number of gastrointestinal eosinophils may vary according to geographic regions and probably correlates with dietary habits [22]. Following main guideline recommendations and experts' suggestions [6], pathologic numbers for paediatric EoGIDs are as follows (Tab. I):

- a peak eosinophil count of ≥ 15 eosinophils in at least one HPF in an esophageal biopsy from at least one site;
- ≥ 30/HPF in ≥ 5 HPF and/or ≥70/HPF in ≥ 3 HPF for stomach;
- ≥ 35/HPF for duodenum, ≥ 37/HPF for ileum and transverse colon, ≥ 40/HPF for cecum, ≥ 52/HPF for ascending colon, ≥ 33/HPF for left colon, ≥ 21/HPF for sigmoid colon and ≥ 19/HPF for rectum.

Importantly, a global evaluation of where eosinophils are found, their interaction with surrounding structures, evidence of degranulation and association with other inflammatory cells is much more important than any precise numeric value. When evaluating gastrointestinal tract biopsies, the number of eosinophils must be considered along with other histologic features like eosinophil distribution in the GI wall, their degranulation, cryptitis and crypt abscesses, other accompanying inflammatory cells, apoptotic bodies, foreign material or microorganisms; these findings, although rarely specific, may be a useful aid to diagnosis.

Table I. Pathologic numbers of eosinophils for pediatric EoGIDs.

Esophagus	≥ 15 in at least 1 HPF		
Stomach	≥ 30/HPF in ≥ 5 HPF and/or ≥ 70/HPF in ≥ 3 HPF		
	Area 1 mm²	**HPF 0.196 mm² (FN 20)**	**HPF 0.238 mm² (FN 22)**
Duodenum	≥ 179	≥ 35	≥ 43
Ileum	≥ 189	≥ 37	≥ 45
Cecum	≥ 204	≥ 40	≥ 49
Ascending colon	≥ 265	≥ 52	≥ 63
Transverse colon	≥ 189	≥ 37	≥ 45
Descending colon	≥ 168	≥ 33	≥ 40
Sigmoid colon	≥ 107	≥ 21	≥ 26
Rectum	≥ 97	≥ 19	≥ 23

Legenda: HPF = High Power Field; FN = Field Number.

The differential diagnosis is broad and cannot be assessed by histologic features alone, including a number of entities that characteristically elicit an eosinophil-predominant response. Laboratory tests, including complete blood, urine and stool examinations for occult blood and cultures for bacteria and parasites, as well as imaging studies, should be evaluated. Only if no other pathologic specific alteration is detected and all other possible causes of a hyper-eosinophilic reaction are excluded, should a diagnosis of primary EoGID be considered. Hypereosinophilic syndrome, usually accompanied by peripheral blood hypereosinophilia, is considered when the peripheral blood eosinophil count is > 1500 × 109 cells/L, which is not typical in primary EoGIDs [23]. Food hypersensitivity and other allergic disorders often induce an eosinophilic reaction in the digestive tract that is morphologically indistinguishable from primary EoGIDs. Different types of infections, mainly parasites and bacteria (e.g. H. pylori is sometimes associated with gastric eosinophilia both before and after treatment) [24,25], may elicit an eosinophil pattern of inflammation in the gastrointestinal mucosa. Many drugs have been reported to induce gastric eosinophilia, the most common being NSAIDs. Eosinophilic inflammation may also be seen in idiopathic inflammatory bowel diseases, celiac disease, connective-tissue diseases, GVHD and malignant neoplasms.

Eosinophilic esophagitis

Eosinophilic oesophagitis (EoE) is the only primary EoGID with diagnostic consensus and the easiest to recognise for pathologists. This is true when a complete and accurate history is given, considering that virtually no eosinophil should be present in the normal esophageal epithelium. EoE is a chronic immune-mediated local inflammatory condition of the oesophagus, considered as a unique form of mixed IgE and non IgE-mediated food allergy, causing dysphagia and food impaction in children and young adults [26]. Epidemiologic data on EoE in the paediatric population vary considerably in different studies, partially due to regional discrepancies, with incidence ranging from 0.7 to 24 per 100,000 children-year [27,28], and a strong male gender predominance.

Although necessary in order to obtain histologic samples, endoscopy alone does not represent a reliable diagnostic tool for EoE, nor is it reliable in assessing disease activity, as up to 25% of patients do not show abnormal endoscopic features[29]. Endoscopic findings in adults include oedema, a whitish exudate coating the mucosa, furrowing (linear lines, longitudinal to the oesophageal axis), concentric rings (so called "trachealisation") and fibro-stenotic strictures, while children may have a normal-appearing oesophagus [8].

Biopsies are mandatory to evaluate the eosinophil-

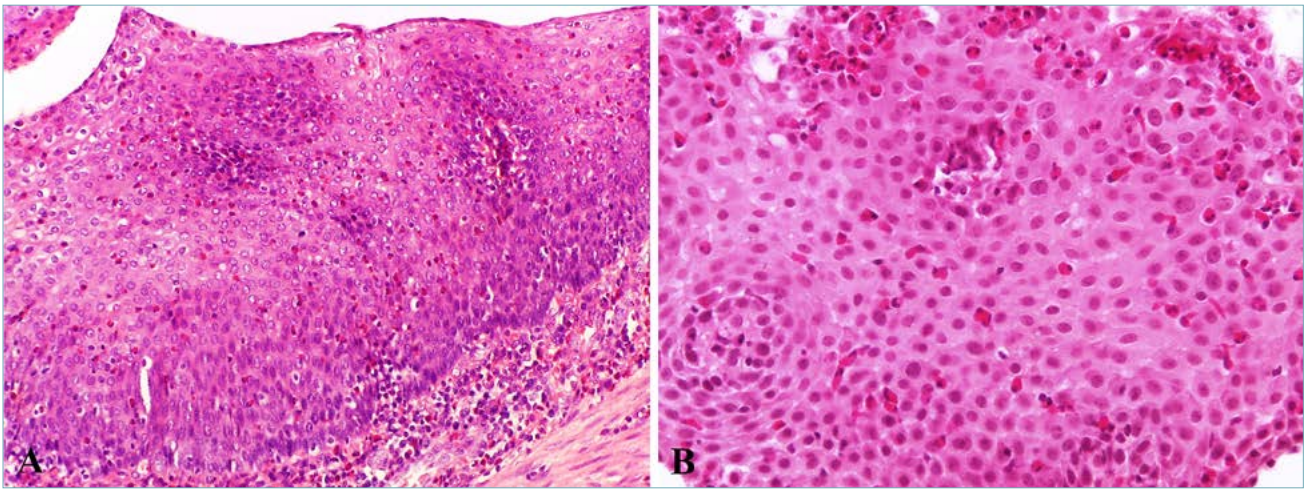

Figure 2. Eosinophilic oesophagitis. (A) Biopsy from proximal esophagus showing basal cell hyperplasia and numerous intraepithelial eosinophils. H&E magnification 20x. (B) Intraepithelial eosinophils are more numerous in superficial layers, often in form of aggregates or microabscesses (B). H&E magnification 40x.

ic infiltrate together with several additional histologic markers. When there is clinical suspicion of EoE and the endoscopic appearance is normal, a minimum of four biopsies should be taken randomly from the proximal and mid oesophagus (this sampling strategy is defined in adult patients and applied to paediatric patients also). However, in order to morphologically exclude reflux oesophagitis, which is the main differential diagnosis in this site, distal oesophageal biopsies should be obtained as well [30]. Endoscopists should focus on areas of abnormality in the mucosa, since they are associated with higher peak eosinophil counts [31].

Histology (Fig. 2) is similar between children and adults, although collagen deposits increase with patient's age [19]. The accepted threshold of intraepithelial eosinophils for the diagnosis of EoE is 15 elements per HPF (independently from field area) [32,33], to be evaluated in hotspots in correctly sampled cases. Alternatively, some studies propose 20-24 eosinophils on a single biopsy [34]. Due to the lack of standardisation of the size of a HPF, eosinophil density should also be reported in mm^2 together with the eosinophil count on HPF [26].

Collins [6] developed a scoring system for adult oesophageal biopsies composed of a constellation of histologic parameters: eosinophil density, eosinophilic abscesses and surface layering, basal zone hyperplasia, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells and lamina propria fibrosis. Summing these morphologic abnormalities, the patient could be better classified in terms of grade and stage (severity and extent). This system may aid in reporting post-treatment EoE histologic changes. Strong data illustrating the natural history of EoE in individual patients are lacking, but a progression from chronic inflammation to a fibro-stenotic phenotype in certain patients has been proposed [35].

The differential diagnosis of paediatric EoE, besides gastroesophageal reflux disease which more frequently affects adults [36], includes: eosinophilic gastroenteritis, hyper-eosinophilic syndrome, Crohn's disease, celiac disease, connective tissue disorders, achalasia, infections, GVHD reactions and causative drugs [37]. Rhinitis, asthma, eczema and both immediate and non-IgE-mediated food allergies are more common in EoE patients compared to the general population. Atopy is a common finding in paediatric atopic dermatitis and EoE, although they are considered as different and independent entities [38].

Alimentary exclusion of sensitized foods has been a cornerstone of therapy in EoE. Empirical methods, like a single-food (milk), a two-food (milk and gluten) or a four-food elimination diet (also avoiding eggs and legumes), show encouraging results, even if more restrictive diet regimens show the best cure rates. In patients demonstrating histologic response, eliminated food groups are sequentially reintroduced while monitoring for disease recurrence by endoscopic biopsies [7]. Proton pump inhibitors are currently the first-line treatment, achieving histologic remission and improvement of symptoms in more than a half of paediatric EoE patients [37]. Topical corticosteroids are effective in decreasing eosinophil-rich mucosal inflammation and in relieving symptoms [39].

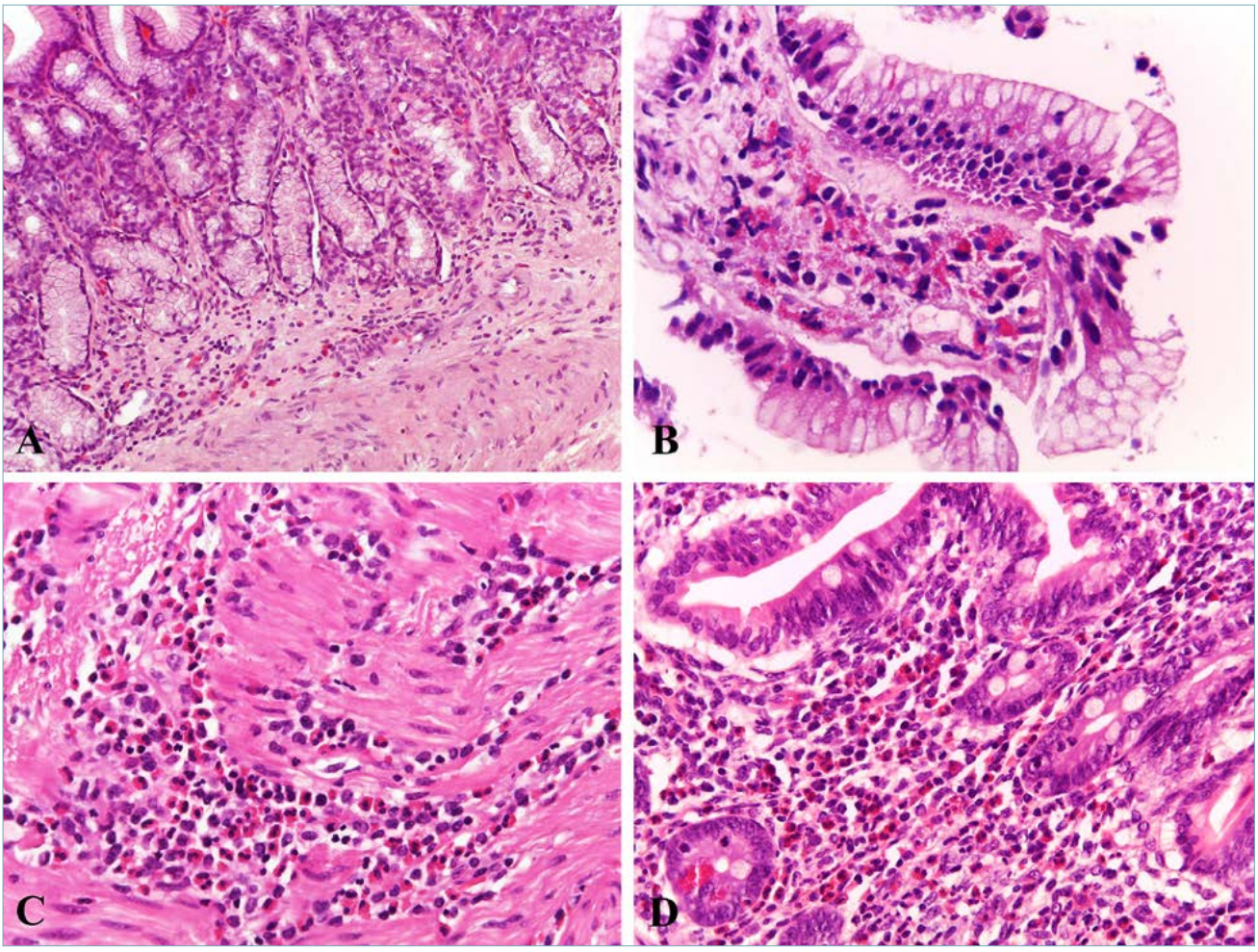

Figure 3. Eosinophilic gastroenteritis. (A) Eosinophilic infiltrate involving the muscularis mucosae in antral gastric biopsy. H&E magnification 10x. (B) Degranulated eosinophils in the lamina propria of the antral mucosa. H&E magnification 40x. (C) Eosinophilic infiltration involving the muscularis propria in a full-thickness biopsy of small bowel. H&E magnification 40x. (D) Dense eosinophilic infiltrate involving the lamina propria of a small bowel endoscopic biopsy. H&E magnification 40x.

Eosinophilic gastroenteritis

The term eosinophilic gastroenteritis (EoGE) should be considered inappropriate as the entire GI tract can be involved, with possible prevalence in the stomach, in the small bowel, or in both and in other rare sites (colon and biliary tract). The clinico-pathologic condition is defined by the histologic demonstration of eosinophilia in the mucosa/wall, associated with gastrointestinal symptoms.

Epidemiologic data are limited; according to a recent American study, the estimated age- and sex-standardized prevalence of EoGE is 8.4/100,000 [40]; of note, the same study reported that eosinophilic gastritis prevalence increases with age (with a peak prevalence in 60 year old patients), while EoGE is more prevalent among children under 5 years old. Patients affected by EoGE also have a higher prevalence of atopic disease such as asthma, allergic rhinitis and atopic dermatitis [41].

Symptoms vary depending on the depth of eosinophilic infiltration in the stomach/bowel wall. The classification proposed by Klein [42] identifies: 1) mucosal involvement, the most common form, usually presenting with abdominal/chest pain, nausea and vomiting; 2) muscularis propria involvement leading to wall thickening and subsequent obstructive symptoms; 3) serosal involvement, the rarest form, associated with eosinophilic ascites. Interestingly, a French study based on 43 patients with a diagnosis of EoGE demonstrated that the serosal form is associated with a single-flare course of disease [43]; contrarily, mucosal involvement

usually presents with a chronic course while the muscular form tends to recurrence.
Endoscopic findings are often normal or non-specific such as erythematous areas, erosions or ulcers, and for this reason, multiple (at least 5-6) biopsies must be taken from random sites and any suspicious lesion [10].
Diagnosis is usually based on endoscopic biopsies, but peritoneal fluid cytology or surgical biopsies may be necessary in order to evaluate muscular and serosal involvement[44]. The widely used approach proposed by Talley is composed of three criteria[45]: presence of gastrointestinal eosinophilia (or peritoneal fluid rich in eosinophils), presence of gastrointestinal symptoms and exclusion of causes of secondary eosinophilia.
In the stomach, there is a lack of consensus concerning the number of eosinophils required to define eosinophilia, the threshold ranging from > 20 eosinophils/HPF [43,46,47] to > 30 eosinophils/HPF [10,48], although thresholds for gastric eosinophilia in children are lacking. Aside from eosinophilia, other histologic features may be found in eosinophilic gastritis: clustering of eosinophils, intra-epithelial eosinophils or intraluminal abscess, glandular destruction and muscularis mucosae involvement [10] (Fig. 3A-B).
In the small bowel, disease may affect the duodenum or other segments of the gastrointestinal tract simultaneously. Histologic features include numerous eosinophils in the lamina propria and infiltrating the surface epithelium and crypts, both as single cells or small clusters with degranulation but rarely with formation of eosinophilic microabscesses (Fig. 3C-D). Intermixed neutrophils, plasma cells and lymphocytes are also present [49].
Similarly to EoE, EoGE is also a diagnosis which requires exclusion of numerous other entities such as: allergic disorders, infections and parasites (especially helminths), hyper-eosinophilic syndrome, celiac disease, Crohn's disease, malignant neoplasms, connective-tissue diseases and GVHD [41,50-52]. Even drug-induced gastrointestinal disorders, much more common in adults, often show mucosal eosinophilia, but due to the non-specificity and variety of histologic patterns, coupled with the lack of clinical data, they are difficult to diagnose by pathologists. Although many medications are associated with gastrointestinal eosinophilia, non-steroidal anti-inflammatory drugs are the most common [53] while other reported drugs include gold salts, carbamazepine, clofazimine, cotrimoxazole, azathioprine, enalapril, gemfibrozil, ipilimumab and chemotherapeutic agents [54-57]. Histologic findings of drug-induced damage are variable and non-specific and include: a reactive epithelial pattern, mucosal infiltration of eosinophils and lymphocytes, increased epithelial apoptosis, melanosis and cytoplasmic vacuolation [50,56,58-60]. Awareness of the temporal relationship between drug intake and onset of symptoms, as well as symptom resolution and histologic regression following discontinuation of the drug, are crucial diagnostic clues [56].
To date there is no consensus on the optimal management strategy of EoGE. Therapeutic algorithms suggest specific allergen avoidance as a first-line treatment and then, if not feasible or ineffective, glucocorticoid therapy, first topical and then systemic [61]. While some studies reported that dietary treatment alone may induce remission of symptoms [41,62] most of the time it is used in combination with corticosteroids [63], leukotriene-receptor antagonists, mast-cell stabilisers, antihistamines, immunomodulators and biologics [64]. In daily practice corticosteroids remain the mainstay of treatment, although often requiring long-term use with its clinical consequences. Moreover, surgery should be considered in cases of perforation or occlusion. One previous study, reviewing 220 EoGE cases, shows that 44% of patients underwent surgical procedures at some stage in their management [62].

Eosinophilic colitis

Eosinophilic colitis (EoC) is a rare disease characterized by a marked increase in eosinophils in the large bowel (Fig. 4). Recent and large epidemiologic data on EoC, recorded by electronic healthcare systems from 26 major integrated U.S. centres [65] reported an overall and paediatric prevalence of 2.1/100,000 and 1.6/100,000 respectively, with a majority of female and Caucasian patients.
Endoscopy usually does not show any grossly visible change; normal mucosa or mucosa with lymphoid nodular hypertrophy have been described. The natural history of paediatric EoC shows a tendency to chronicity with periods of activity and periods of apparent remission [66]. Three cases of pseudo-obstruction of the colon, probably related to ganglionitis-induced dysmotility, have been reported [67].
The eosinophil count should be performed on selected hotspot fields, avoiding lymphoid follicles. For practical reasons eosinophil density is usually estimated by counting the number of eosinophils in three or more high-power microscopic fields and calculating the mean [68]. In addition to the total eosinophil number, other important features include: eosinophil degranulation, aggregation, cryptitis and formation of microabscesses.
Allergy to cow's milk is considered the main cause of eosinophilic colitis and its elimination from the diet of the lactating mother or from the infant's diet is generally an effective therapeutic measure [67]. Causes that may result in secondary eosinophilic colitis are inflammato-

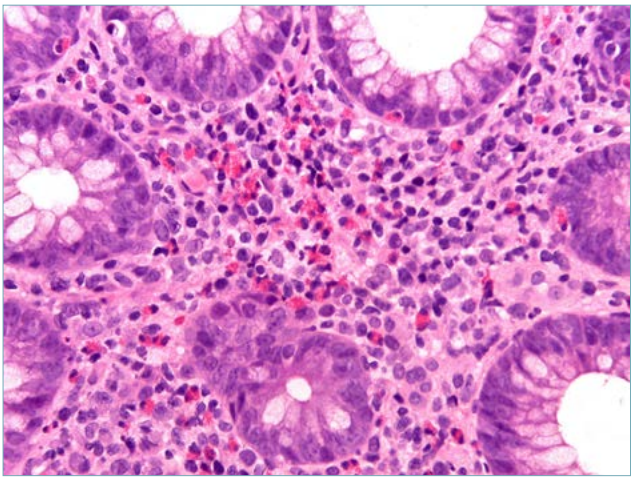

Figure 4. Eosinophilic colitis. Presence of numerous eosinophils, in aggregate and sheets in the lamina propria and infiltrating the crypt epithelium. H&E magnification 40x.

ry bowel diseases, parasitic infections (from helminths and protozoa) [69,70], allergies and drug-induced reactions (clozapine, carbamazepine, rifampicin, non-steroidal anti-inflammatory agents, tacrolimus, and gold salts). Autoimmune connective tissue diseases as well as bone marrow transplantation and neoplasms must be also considered. EoC remains a diagnosis of exclusion, even with massive presence of eosinophils.

Conclusions

The pathologist must choose their words carefully when assessing the nature of an eosinophil-rich infiltrate of the digestive tract. Reports should not include a diagnosis of primary EoGID if clinical data and laboratory, radiological and endoscopic results are not available, thus not permitting other forms of gastrointestinal eosinophilia to be ruled out. A more descriptive definition with the specification of "with eosinophilic pattern" should be favored in order to avoid potential confusion between different entities.

References

1 Koutri E, Papadopoulou A. Eosinophilic Gastrointestinal Diseases in Childhood. Ann Nutr Metab 2018;73:18-28. https://doi.org/https://doi.org/10.1159/000493668

2 Pesek RD, Reed CC, Muir AB, et al. Increasing Rates of Diagnosis, Substantial Co-Occurrence, and Variable Treatment Patterns of Eosinophilic Gastritis, Gastroenteritis, and Colitis Based on 10-Year Data Across a Multicenter Consortium. Am J Gastroenterol 2019;114:984-994. https://doi.org/https://doi.org/10.14309/ajg.0000000000000228

3 Yantiss RK. Eosinophils in the GI tract: how many is too many and what do they mean? Mod Pathol 2015;28:S7-S21. https://doi.org/https://doi.org/10.1038/modpathol.2014.132

4 Koutri E, Patereli A, Noni M, et al. Distribution of eosinophils in the gastrointestinal tract of children with no organic disease. Ann Gastroenterol 2020;33:508-515. https://doi.org/https://doi.org/10.20524/aog.2020.0518

5 Egritas Gurkan O, Ozturk H, Karagol HIE, et al. Primary Eosinophilic Gastrointestinal Diseases Beyond Eosinophilic Esophagitis in Children. J Pediatr Gastroenterol Nutr 2021;72:294-299. https://doi.org/https://doi.org/10.1097/MPG.0000000000002925

6 Collins MH, Capocelli K, Yang GY. Eosinophilic Gastrointestinal Disorders Pathology. Front Med 2018;4:261. https://doi.org/https://doi.org/10.3389/fmed.2017.00261

7 Gonsalves N. Eosinophilic Gastrointestinal Disorders. Clin Rev Allergy Immunol 2019;57:272-285. https://doi.org/https://doi.org/10.1007/s12016-019-08732-1

8 Lucendo AJ. Eosinophilic diseases of the gastrointestinal tract. Scand J Gastroenterol 2010;45:1013-1021. https://doi.org/https://doi.org/10.3109/00365521003690251

9 Matsushita T, Maruyama R, Ishikawa N, et al. 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 2015;39:521-527. https://doi.org/https://doi.org/10.1097/PAS.0000000000000370

10 Lwin T, Melton SD, Genta RM. Eosinophilic gastritis: histopathological characterization and quantification of the normal gastric eosinophil content. Mod Pathol 2011;24:556-563. https://doi.org/https://doi.org/10.1038/modpathol.2010.221

11 Walker MM, Salehian SS, Murray CE, et al. Implications of eosinophilia in the normal duodenal biopsy - an association with allergy and functional dyspepsia. Aliment Pharmacol Ther 2010;31:1229-1236. https://doi.org/https://doi.org/10.1111/j.1365-2036.2010.04282.x

12 Turner KO, Sinkre RA, Neumann WL, et al. Primary Colonic Eosinophilia and Eosinophilic Colitis in Adults. Am J Surg Pathol 2017;41:225-233. https://doi.org/https://doi.org/10.1097/PAS.0000000000000760

13 Saad AG. Normal quantity and distribution of mast cells and eosinophils in the pediatric colon. Pediatr Dev Pathol 2011;14:294-300. https://doi.org/https://doi.org/10.2350/10-07-0878-OA.1

14 Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol 2018;141:41-58. https://doi.org/https://doi.org/10.1016/j.jaci.2017.11.003

15 Shah N, Foong RM, Borrelli O, et al. Histological findings in infants with Gastrointestinal food allergy are associated with specific gastrointestinal symptoms; retrospective review from a tertiary centre. BMC Clin Pathol 2015;15:12. https://doi.org/https://doi.org/10.1186/s12907-015-0012-6

16 Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. Nutrients 2020;12:2086. https://doi.org/https://doi.org/10.3390/nu12072086

17 Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2017;139:1111-1126.e4. https://doi.org/https://doi.org/10.1016/j.jaci.2016.12.966

18 Caubet JC, Szajewska H, Shamir R, et al. Non-IgE-mediated gastrointestinal food allergies in children. Pediatr Allergy Immunol 2017;28:6-17. https://doi.org/https://doi.org/10.1111/pai.12659

[19] Visaggi P, Savarino E, Sciume G, et al. Eosinophilic esophagitis: clinical, endoscopic, histologic and therapeutic differences and similarities between children and adults. Therap Adv Gastroenterol 2021;14:1756284820980860. https://doi.org/https://doi.org/10.1177/1756284820980860

[20] Conner JR, Kirsch R. The pathology and causes of tissue eosinophilia in the gastrointestinal tract. Histopathology 2017;71:177-199. https://doi.org/https://doi.org/10.1111/his.13228

[21] Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol 2018;3:271-280. https://doi.org/https://doi.org/10.1016/S2468-1253(18)30005-0

[22] Pascal RR, Gramlich TL, Parker KM, et al. Geographic variations in eosinophil concentration in normal colonic mucosa. Mod Pathol 1997;10:363-365.

[23] Diaz-Oliva SE, Aguilera-Matos I, Villa Jiménez OM, et al. Oesophageal eosinophilia and oesophageal diseases in children: are the limits clear? BMJ Paediatr Open 2020;4:e000680. https://doi.org/https://doi.org/10.1136/bmjpo-2020-000680

[24] Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1175-1183. https://doi.org/https://doi.org/10.1016/j.cgh.2007.05.015

[25] Papadopoulos AA, Tzathas C, Polymeros D, et al. Symptomatic eosinophilic gastritis cured with Helicobacter pylori eradication. Gut 2005;54:1822. https://doi.org/https://doi.org/10.1136/gut.2005.075077

[26] Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5:335-358. https://doi.org/https://doi.org/10.1177/2050640616689525

[27] Soon IS, Butzner JD, Kaplan GG, et al. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr 2013;57:72-80. https://doi.org/https://doi.org/10.1097/MPG.0b013e318291fee2

[28] Robson J, O'Gorman M, McClain A, et al. Incidence and Prevalence of Pediatric Eosinophilic Esophagitis in Utah Based on a 5-Year Population-Based Study. Clin Gastroenterol Hepatol 2019;17:107-114.e1. https://doi.org/https://doi.org/10.1016/j.cgh.2018.06.028

[29] Dellon ES, Cotton CC, Gebhart JH, et al. Accuracy of the Eosinophilic Esophagitis Endoscopic Reference Score in Diagnosis and Determining Response to Treatment. Clin Gastroenterol Hepatol 2016;14:31-39. https://doi.org/https://doi.org/10.1016/j.cgh.2015.08.040

[30] Nielsen JA, Lager DJ, Lewin M, et al. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. Am J Gastroenterol 2014;109:515-520. https://doi.org/https://doi.org/10.1038/ajg.2013.463

[31] Salek J, Clayton F, Vinson L, et al. Endoscopic appearance and location dictate diagnostic yield of biopsies in eosinophilic oesophagitis. Aliment Pharmacol Ther 2015;41:1288-1295. https://doi.org/https://doi.org/10.1111/apt.13201

[32] Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3-22. https://doi.org/https://doi.org/10.1016/j.jaci.2011.02.040

[33] Mastracci L, Grillo F, Parente P, et al. Non gastro-esophageal reflux disease related esophagitis: an overview with a histologic diagnostic approach. Pathologica 2020;112:128-137. https://doi.org/https://doi.org/10.32074/1591-951X-156

[34] Gunasekaran TS, Chu C, Ronquillo N Jr, et al. Detailed Histologic Evaluation of Eosinophilic Esophagitis in Pediatric Patients Presenting with Dysphagia or Abdominal Pain and Comparison of the Histology between the Two Groups. Can J Gastroenterol Hepatol 2017;2017:3709254. https://doi.org/https://doi.org/10.1155/2017/3709254

[35] Koutlas NT, Dellon ES. Progression from an Inflammatory to a Fibrostenotic Phenotype in Eosinophilic Esophagitis. Case Rep Gastroenterol 2017;11:382-388. https://doi.org/https://doi.org/10.1159/000477391

[36] Mastracci L, Grillo F, Parente P, et al. Gastro-esophageal reflux disease and Barrett's esophagus: an overview with an histologic diagnostic approach. Pathologica 2020;112:117-127. https://doi.org/https://doi.org/10.32074/1591-951X-162

[37] Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology 2018;155:1022-1033.e10. https://doi.org/https://doi.org/10.1053/j.gastro.2018.07.009

[38] Hopp RJ. Eosinophilic Esophagitis in Pediatrics: The Worst of all Possible Allergy Worlds? J Allergy (Cairo). 2012;2012:179658. https://doi.org/https://doi.org/10.1155/2012/179658

[39] Munoz-Persy M, Lucendo AJ. Treatment of eosinophilic esophagitis in the pediatric patient: an evidence-based approach. Eur J Pediatr 2018;177:649-663. https://doi.org/https://doi.org/10.1007/s00431-018-3129-7

[40] Jensen ET, Martin CF, Kappelman MD, et al. Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database. J Pediatr Gastroenterol Nutr 2016;62:36-42. https://doi.org/https://doi.org/10.1097/MPG.0000000000000865

[41] Ko HM, Morotti RA, Yershov O, et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. Am J Gastroenterol 2014;109:1277-1285. https://doi.org/https://doi.org/10.1038/ajg.2014.166

[42] Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. Medicine (Baltimore) 1970;49:299-319. https://doi.org/https://doi.org/10.1097/00005792-197007000-00003

[43] Pineton de Chambrun G, Gonzalez F, Canva JY, et al. Natural history of eosinophilic gastroenteritis. Clin Gastroenterol Hepatol 2011;9:950-956.e1. https://doi.org/https://doi.org/10.1016/j.cgh.2011.07.017

[44] Pineton de Chambrun G, Dufour G, Tassy B, et al. Diagnosis, Natural History and Treatment of Eosinophilic Enteritis: a Review. Curr Gastroenterol Rep 2018;20:37. https://doi.org/https://doi.org/10.1007/s11894-018-0645-6

[45] Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut 1990;31:54-58. https://doi.org/https://doi.org/10.1136/gut.31.1.54

[46] Chang JY, Choung RS, Lee RM, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. Clin Gastroenterol Hepatol 2010;8:669-e88. https://doi.org/https://doi.org/10.1016/j.cgh.2010.04.022

[47] Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Dig Liver Dis 2015;47:197-201. https://doi.org/https://doi.org/10.1016/j.dld.2014.11.009

[48] Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol 2018;3:271-280. https://doi.org/https://doi.org/10.1016/S2468-1253(18)30005-0

[49] Serra S, Jani PA. An approach to duodenal biopsies. J Clin Pathol 2006;59:1133-1150. https://doi.org/https://doi.org/10.1136/jcp.2005.031260

[50] Mueller S. Classification of eosinophilic gastrointestinal diseases. Best Pract Res Clin Gastroenterol 2008;22(3):425-440. https://doi.org/https://doi.org/10.1016/j.bpg.2007.12.008

[51] Parente P, Pastore M, Grillo F, et al. Very Early Onset-IBD: evidence for the need of a multidisciplinary approach [published online ahead of print, 2021 Dec 2]. Pathologica 2021;10.32074/1591-951X-336. https://doi.org/https://doi.org/10.32074/1591-951X-336

[52] Parente P, Mastracci L, Vanoli A, et al. Pattern-based Histologic Approach in Very Early Onset IBD: Main Features and Differential Diagnosis. Adv Anat Pathol 2021;10.1097/PAP.0000000000000323. https://doi.org/https://doi.org/10.1097/PAP.0000000000000323

[53] Philpott HL, Nandurkar S, Lubel J, et al. Drug-induced gastrointestinal disorders. Postgrad Med J 2014;90(1065):411-419. https://doi.org/https://doi.org/10.1136/postgradmedj-2013-100316rep

[54] Grattagliano I, Ubaldi E, Portincasa P. Drug-induced enterocolitis: Prevention and management in primary care. J Dig Dis 2018;19:127-135. https://doi.org/https://doi.org/10.1111/1751-2980.12585

[55] Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. Immunol Allergy Clin North Am 2007;27:443-455. https://doi.org/https://doi.org/10.1016/j.iac.2007.06.002

[56] De Petris G, Gatius Caldero S, Chen L, et al. Histopathological changes in the gastrointestinal tract due to drugs: an update for the surgical pathologist (part I of II). Int J Surg Pathol 2014;22:120-128. https://doi.org/https://doi.org/10.1177/1066896913502229

[57] De Petris G, Caldero SG, Chen L, et al. Histopathological changes in the gastrointestinal tract due to medications: an update for the surgical pathologist (part II of II). Int J Surg Pathol 2014;22:202-211. https://doi.org/https://doi.org/10.1177/1066896913502230

[58] Lee FD. Drug-related pathological lesions of the intestinal tract. Histopathology 1994;25:303-308. https://doi.org/https://doi.org/10.1111/j.1365-2559.1994.tb01347.x

[59] Price AB. Pathology of drug-associated gastrointestinal disease. Br J Clin Pharmacol 2003;56:477-482. https://doi.org/https://doi.org/10.1046/j.1365-2125.2003.01980.x

[60] De Petris G, De Marco L, López JI. Drug-induced gastrointestinal injury (DIGI). Updates, reflections and key points. Pathologica. 2017;109:97-109.

[61] Hogan SP, Rothenberg ME. Review article: The eosinophil as a therapeutic target in gastrointestinal disease. Aliment Pharmacol Ther 2004;20:1231-1240. https://doi.org/https://doi.org/10.1111/j.1365-2036.2004.02259.x

[62] Yamada Y, Kato M, Isoda Y, et al. Eosinophilic gastroenteritis treated with a multiple-food elimination diet. Allergol Int 2014;63:53-56. https://doi.org/https://doi.org/10.2332/allergolint.13-LE-0633

[63] Pesek RD, Gupta SK. Future therapies for eosinophilic gastrointestinal disorders. Ann Allergy Asthma Immunol 2020;124:219-226. https://doi.org/https://doi.org/10.1016/j.anai.2019.11.018

[64] Chen PH, Anderson L, Zhang K, et al. Eosinophilic Gastritis/Gastroenteritis. Curr Gastroenterol Rep 2021;23:13. https://doi.org/https://doi.org/10.1007/s11894-021-00809-2

[65] Mansoor E, Saleh MA, Cooper GS. Prevalence of Eosinophilic Gastroenteritis and Colitis in a Population-Based Study, From 2012 to 2017. Clin Gastroenterol Hepatol 2017;15:1733-1741. https://doi.org/https://doi.org/10.1016/j.cgh.2017.05.050

[66] Alfadda AA, Storr MA, Shaffer EA. Eosinophilic colitis: epidemiology, clinical features, and current management. Therap Adv Gastroenterol 2011;4:301-309. https://doi.org/https://doi.org/10.1177/1756283X10392443

[67] Schäppi MG, Smith VV, Milla PJ, et al. Eosinophilic myenteric ganglionitis is associated with functional intestinal obstruction. Gut 2003;52:752-755. https://doi.org/https://doi.org/10.1136/gut.52.5.752

[68] Bates AW. Diagnosing eosinophilic colitis: histopathological pattern or nosological entity? Scientifica 2012;2012:682576. https://doi.org/https://doi.org/10.6064/2012/682576

[69] Di Tommaso LA, Rosenberg CE, Eby MD, et al. Prevalence of eosinophilic colitis and the diagnoses associated with colonic eosinophilia. J Allergy Clin Immunol 2019;143:1928-1930.e3. https://doi.org/https://doi.org/10.1016/j.jaci.2018.12.1002

[70] Grillo F, Campora M, Carlin L, et al. “Stranger things” in the gut: uncommon items in gastrointestinal specimens. Virchows Arch 2021;10.1007/s00428-021-03188-1. https://doi.org/https://doi.org/10.1007/s00428-021-03188-1