Review Articles

Eosinophilic gastrointestinal disorders

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Abstract

Eosinophilic gastrointestinal disorders are rare inflammatory diseases of unknown origin defined as disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia (eg, drug reactions, parasitic infections, and malignancy). Eosinophil levels fluctuate, predating presentation by years and may be absent at presentation.

Allergic mechanism has been suggested in at least a subset of patients. Indeed, increased total IgE and food-specific IgE levels have been detected in the majority of patients. A majority of patients have positive skin test responses to a variety of food antigens but do not have typical anaphylactic reactions, which is consistent with a delayed-type of food hypersensitivity syndrome.

A male preponderance in the third to fifth decades of life has been reported. 25% have a history of atopy. Presentation may vary from a single organ affected by eosinophilic infiltrate to that of multisystem involvement. The gastric antrum and proximal small bowel are the most affected sites, commonly presenting with obstruction. Frank ulceration and haemorrhage are unusual. Symptoms are non-specific with nausea, vomiting, dyspepsia, abdominal pain, and weight loss. Approximately 80% have symptoms for several years before diagnosis. Eosinophilic gastroenteritis can present with protein-losing enteropathy. Serosal inflammation is the most likely cause of the exudative ascites. Biliary obstruction is a rare presentation of eosinophilic gastroenteritis. Presentation can mimic malignancy.

Ultrasound, computed tomography and contrast studies may show nonspecific features of thickened mucosa and bowel wall. The histology is characteristic with mucosal oedema, a dense eosinophilic infiltrate, muscle bundle hypertrophy, and fibrosis. The submucosa is most commonly affected and full thickness biopsies may be needed for diagnosis.

Treatments are often unsatisfactory, and long-term outcomes are uncertain. Prednisolone 20–40 mg per day remains an empirical treatment. Elimination diets and sodium cromoglycate are successful in rare cases where the causative antigen is isolated. Drugs such as montelukast, ketotifen, suplatast tosilate, mycophenolate mofetil, and alternative chinese medicines have been advocated but are generally not successful. Spontaneous resolution may occur. It is hoped that a better understanding of the pathogenesis and treatment of EG will emerge by combining holistic clinical and research approaches involving experts in the fields of allergy, gastroenterology, nutrition, and pathology.

Keywords: Eosinophilic Gastroenteritis, Mast cell stabilizers, leukotriene receptor antagonists.

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Epidemiology

Eosinophilic Gastrointestinal Disorders (EGD) is a rare inflammatory disease. [1] EGD are diseases characterized by exacerbations and remissions. [2] Kaijser was probably the first to report a patient with EG in 1937; since then, the number of case reports has increased, and the incidence is difficult to estimate. [3] Although cases have been reported worldwide, the exact incidence of EGE is unclear. [4] An allergic disorder is present in approximately one-half of the patients. [5] Several epidemiologic and clinical features suggest an allergic component. [6] Approximately, one-half of patients have allergic disease, such as asthma, defined food sensitivities, eczema, or rhinitis. [7] Some patients have elevated serum IgE levels. [8] Rare patients have IgE antibodies directed against specific foods, such as bovine serum albumin. Extensive studies have failed to identify a reproducible allergic reaction to specific foods in all patients, and patients with EG generally have normal responses to standard mitogens such as pokeweed and phytohemagglutinin. [9] Thus, the role of allergy as a stimulus for the recruitment of eosinophils to the gastrointestinal tract remains controversial. [10]

Patients present clinically in the third to fifth decades of life; the average age of onset is 37 years, but the disease can affect any age group, from infancy through to the seventh decade. [11] Men are most affected (sex ratio 9:1). [12]

Pathogenesis

The cause of EGD is not clear, but the condition is closely associated with atopic disorders, and there is evidence that both IgE- and non-IgE-mediated food allergy mechanisms are involved in its aetiology. [13] Foods commonly implicated include cow milk, soya, wheat and egg. [14]

Evidence in support of the concept that EG arise as a result of the interplay of genetic and environmental factors is accumulating. [15]

Notably, a large percentage (approximately 10%) of patients with EG has an immediate family member with an EGD. [16] Additionally, several lines of evidence support an allergic cause, including the finding that approximately 75% of patients with EG are atopic, [17] the finding that the severity of disease can sometimes be reversed by institution of an allergen-free diet, and the common finding of mast cell degranulation in tissue specimens. [18] Importantly, our recent models of EG support a potential allergic cause for these disorders. [19] Interestingly, despite the common finding of food-specific IgE in patients with EG, food-induced anaphylactic responses only occur in a minority of patients. [20] Thus EGD have properties that fall between pure IgE-mediated food allergy and cellular-mediated hypersensitivity disorders (eg, celiac disease). [21] Although the incidence of primary EG has not been rigorously calculated, a miniepidemic of these diseases has been noted over the last decade. [22] EGD typically occur independent of peripheral blood eosinophilia (>50% of the time), indicating the potential significance of gastrointestinal-specific mechanisms for regulating eosinophil levels; indeed, some authors have demonstrated the importance of the eotaxin pathway in this process. [23] However, some patients with EG can have substantially increased levels of peripheral blood eosinophils and meet the diagnostic criteria for the idiopathic hypereosinophilic syndrome (HES). [24] Notably, although HES commonly involves the gastrointestinal tract, the other end organs typically associated with HES (eg, heart and skin) are uncommonly involved in EGD. [25]

Eosinophil accumulation in the gastrointestinal tract is a common feature of eosinophilic gastroenteritis. [26] The underlying molecular mechanism predisposing to the clinical manifestation of EGD is unknown. The disorder is classified into primary and secondary subtypes.[27] The primary subtype, which has also been called idiopathic or allergic EGD, includes the atopic, nonatopic, and familial subtypes. [28]

In-clinical studies increased secretion of IL-4 and IL-5 by peripheral blood T cells has been reported in patients with eosinophilic gastroenteritis. [29] Furthermore, T cells derived from the lamina propria of the duodenum of patients with EGD preferentially secrete T_H2 cytokines (especially IL-13) when stimulated with milk proteins. [30] IgA deficiency has also been associated with eosinophilic gastroenteritis; it is interesting to speculate that this could be related to the associated increased rate of atopy in these patients or to an occult gastrointestinal infection in these patients. [31]

Eosinophils are pleiotropic cells stimulated by a variety of triggers. *In vitro* studies have shown that eosinophil granule constituents are toxic to a variety of tissues, including intestinal epithelium.[23] Eosinophil granules contain a crystalloid core composed of Major Basic Protein (MBP) 1 (and MBP-2) and a matrix composed of Eosinophil Cationic Protein (ECP), Eosinophil-Derived Neurotoxin (EDN), and Eosinophil Peroxidase (EPO). [33] These cationic proteins share certain pro-inflammatory properties but differ in other ways. For example, MBP, EPO, and ECP have cytotoxic effects on epithelium in concentrations similar to those found in biologic fluids from patients with eosinophilia. [34] Additionally, ECP and EDN belong to the ribonuclease A superfamily and possess antiviral and ribonuclease activity. ECP can insert voltage-insensitive, ion-nonselective toxic pores into the membranes of target cells, and these pores might facilitate the entry of other toxic molecules. MBP directly increases smooth muscle reactivity by causing dysfunction of vagal muscarinic M2 receptors. [35] MBP also triggers degranulation of mast cells and basophils. [36] Triggering of eosinophils through engagement of receptors for cytokines, immunoglobulins, and complement can lead to the generation of a wide range of inflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-13, GM-CSF, transforming growth factors, TNF-α, macrophage inflammatory protein 1α, vascular endothelial cell growth factor, and eotaxin 1, indicating that they have the potential to modulate multiple aspects of the immune response. [37]

In fact, eosinophil-derived transforming growth factor β is linked with epithelial growth, fibrosis, and tissue remodeling. Eosinophils express MHC class II molecules and relevant co-stimulatory molecules (CD40, CD28, B7.1, and B7.2) and secrete an array of cytokines capable of promoting lymphocyte proliferation, activation, and T Helper (T_H1) or T_H2 polarization (IL-2, IL-4, IL-6, IL-12, and IL-10). [38] Further eosinophil-mediated damage is caused by toxic hydrogen peroxide and halide acids generated by EPO and by superoxide generated by the respiratory burst oxidase enzyme pathway in eosinophils. [39] Eosinophils also generate large amounts of cysteinyl LTC_4, which is metabolized to LTD_4 and LTE_4. [40] These 3 lipid mediators increase vascular permeability and mucus secretion and are potent stimulators of smooth muscle contraction. [41] Clinical investigations have demonstrated extracellular deposition of MBP and ECP in the small bowel of patients with eosinophilic gastroenteritis and have shown a correlation between the level of eosinophils and disease severity. [42] Electron microscopy studies have revealed ultrastructural changes in the secondary granules (indicative of eosinophil degranulation and mediator release) in duodenal samples from patients with eosinophilic gastroenteritis. [43] Furthermore, Charcot-Leyden crystals, remnants of eosinophil degranulation, are commonly found on microscopic examination of stools obtained from patients with eosinophilic gastroenteritis. [44]

Eosinophilic Esophagitis (EO)

An isolated eosinophilic inflammation of the oesophagus is the most common of the eosinophilic gastrointestinal disorders[(45)]. EO is of increasing clinical significance in many developed countries, in parallel with the recent increase in food allergic disorders. The estimated prevalence in the US population aged between 0–19 years is even higher, at 4.3 cases per 10 000 individuals. [46]

Clinical features: Patients present with symptoms indistinguishable from those of Gastro-Oesophageal Reflux (GOR); however, unlike people with GOR, they are generally unresponsive to treatment with proton pump inhibitors (Level III-2). Infants often have additional clinical features, including feeding difficulties, feeding refusal and/or poor weight gain. [47] In older children and adults, oesophageal food impaction is the most characteristic symptom (Level III-3), and should alert clinicians to include EO in the differential diagnosis. [48] Typically, patients with EO have associated atopic disorders, including asthma and eczema. [49]

Diagnosis: The diagnostic hallmark of EO is a dense, eosinophilic infiltrate involving the entire oesophageal mucosa, which is normally free of eosinophils. Key diagnostic criteria are basal layer hyperplasia and the presence of more than 20 eosinophils per high power field (× 400 magnification) in gastroscopic biopsies of the lower and upper oesophagus (Level III-3). [50] Although oesophageal eosinophils are also seen in patients with reflux oesophagitis, mucosal eosinophil counts in such patients are lower (< 5 per high power field), and the eosinophils are limited to the lower oesophagus. There is a typical mucosal appearance in many patients with EO (thickened mucosa, with longitudinal furrowing and superficial white plaques)- although in about a third of patients the mucosa will look macroscopically normal. [51]

Skin Prick Testing (SPT) and Atopy Patch Testing (APT) (the application of food or food extracts to the skin for 48 hours) are thought to be helpful in identifying potential causative food allergens, but prospective studies are needed to evaluate their predictive value. [52]

Treatment and Natural History: Until this point, most studies on treatment and follow-up of eosinophilic esophagitis have been in the order of months to a few years in small populations of patients. [53]

Short-term trials have mostly advocated the use of inhaled steroids (fluticasone) and food avoidance therapies, but long-term trials are desperately needed to elucidate the time course needed for these treatments. This is particularly important in light of one long-term follow-up study in adults demonstrating little improvement and common progression of the disease. [54] There is a good effect of oral or inhaled steroids on symptoms and on the reduction of esophageal eosinophilia. In contrast, the use of rigid food avoidance based on skin prick and patch testing, and more drastically, the use of an amino-acid based elemental formula, proved a far more durable therapy as regard to the reduction of symptoms and the normalization of esophageal biopsy. [55] As expected, however, reintroduction of problem foods resulted in a clinical and tissue relapse in most patients. One of the concerns in fully embracing dietary restriction as the dominant therapy for eosinophilic esophagitis is in the reliability and type of testing that should be used to identify these allergens. For example, skin prick testing alone when used to dictate diet therapy may not be reliable for predicting response in eosinophilic esophagitis for a majority of patients. Whether we will be able to use these or other tests to approach uniform reliability in tailoring diet therapy or make it more tolerable to eosinophilic esophagitis patients has yet to be determined. [56]

Prognosis

The long-term prognosis for EO is largely unknown. [57] In some infants and young children with food protein-induced EO, the disease may remit due to development of oral tolerance to the offending food protein. [58] However, EO usually follows a chronic relapsing course. Up to date, no studies have shown an increased risk of malignancy in patients with EO, but there is evidence that uncontrolled chronic eosinophilic inflammation may cause subepithelial fibrosis and remodelling, which eventually may cause obstructive dysphagia, strictures or persistent oesophageal narrowing. [59]

Eosinophilic Gastritis and Gastroenteritis

In contrast to the esophagus, the stomach and intestine have readily detectable baseline eosinophils under healthy conditions. [60] As such, the diagnosis of eosinophilic gastritis, enteritis, and gastroenteritis is even more complex than EE. In this review, eosinophilic gastritis, enteritis, and gastroenteritis are grouped together because they are clinically similar and because there is a paucity of information available concerning their pathogenesis; however, it is likely that they are indeed distinct entities in most patients. [61] These diseases are characterized by the selective infiltration of eosinophils in the stomach, small intestine, or both, with variable involvement of the esophagus, large intestine, or both. It is now appreciated that many disorders are accompanied by eosinophil infiltration in the stomach, such as parasitic and bacterial infections (including *Helicobacter pylori*), IBD, HES, myeloproliferative disorders, periarteritis, allergic vasculitis, scleroderma, drug injury, and drug hypersensivity. [62] Similar to EE, these disorders are classified into primary and secondary subtypes. The primary subtype includes the atopic, nonatopic, and familial variants, whereas the secondary subtype is divided into 2 groups, one composed of systemic eosinophilic disorders (HES) and the other composed of noneosinophilic disorders. [63] Primary eosinophilic enteritis, gastritis, and gastroenteritis have also been called idiopathic or allergic gastroenteropathy.[64] Primary eosinophilic gastroenteritis encompasses multiple disease entities subcategorized into 3 types on the basis of the level of histologic involvement: mucosal, muscularis, and serosal forms. Of note, either layer of the gastrointestinal tract can be involved, so that endoscopic biopsy can be normal in patients with the muscularis subtype, serosal subtype, or both. [65]

Clinical picture: Eosinophilic gastro-enteritis most often involves the stomach and the small bowel. Approximately, 50% of patients have a history of atopy (hay fever, asthma, food allergy). [66] In children, a history of allergy is even more common. [67]

The clinical presentation of EG is determined by the site and depth of eosinophilic intestinal infiltration; The mucosal form of EG (most common variant) is characterized by vomiting, dyspepsia, abdominal pain (that can even mimic acute appendicitis), diarrhea, blood loss in the stools, iron deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive.[68] The muscularis form is characterized by infiltration of eosinophils predominantly in the muscularis layer, leading to thickening of the bowel wall, which may present with gastrointestinal obstructive symptoms mimicking pyloric stenosis or gastric outlet syndrome. [69] The eosinophilic involvement often is localized to the stomach but can involve small bowel. Cramping and abdominal pain associated with nausea and vomiting occur frequently. [70] Food allergy and past-history of allergy are less common in these patients than in patients with mucosal layer disease. [71] In serosal form, which is the least common form of the disease, the entire GI wall usually is involved. These patients typically present with significant bloating, eosinophilic ascites and higher peripheral eosinophil counts compared with the other forms. Serosal and visceral peritoneal inflammation leads to leakage of fluids. [72]

Children and adolescents can present with growth retardation, failure to thrive, delayed puberty, or amenorrhea. [73]

Diagnosis

No standards for the diagnosis of eosinophilic gastroenteritis exist, but a few findings support the diagnosis. [74] For example, the presence of increased eosinophils in biopsy specimens from the gastrointestinal tract wall, the infiltration of eosinophils within intestinal crypts and gastric glands, the lack of involvement of other organs, and the exclusion of other causes of eosinophilia (eg, infections and IBD) are supportive of eosinophilic gastroenteritis. [75] Histologic analysis

of the small bowel from patients with these disorders reveals extracellular deposition of eosinophil granule constituents, and indeed, extracellular MBP and ECP are immunohistochemically detectable at increased levels. [76] Patients with eosinophilic gastritis can have micronodules (and/or polyposis) noted on endoscopy, and these lesions often contain marked aggregates of lymphocytes and eosinophils. [77] Food allergy and peripheral eosinophilia are not required for diagnosis, but up to 50% of patients with the mucosal form had a history of food allergy or intolerance. [78]

EG should be suspected in a patient with any gastrointestinal symptoms associated with peripheral eosinophilia. It should also be considered before making a diagnosis of irritable bowel syndrome. The diagnosis of EG can be made in almost all cases by suspicion in the appropriate clinical context and endoscopic or full thickness biopsy or paracentesis. [79] Other diseases in which gastrointestinal symptoms are associated with peripheral eosinophilia usually can be distinguished from EG with simple laboratory tests and or endoscopic biopsies: Intestinal parasites such as Ancylostoma, Anisakis, Ascaris, Strongyloides, Toxicara, Trichura, Capillaria, and Trichinella all cause eosinophilia and should be excluded with careful examination of the stool for ova or parasites. [80] Skin sensitivity tests for these parasites are available in some countries but are of uncertain accuracy. Malignancies, such as lymphoma, gastric cancer, and colon cancer, can present with obstruction, masses on barium radiography, and eosinophilia. Crohn's disease can usually be excluded by biopsy because it lacks the florid eosinophilic infiltration of the bowel. Rarely, Crohn's colitis or ulcerative colitis may be associated with peripheral eosinophilia. Polyarteritis nodosa is associated with systemic manifestations, markedly elevated erythrocyte sedimentation rate, and perivascular eosinophilia. Hypereosinophilic syndrome (HES) is an idiopathic condition associated with marked peripheral eosinophilia and gastroenteritis. [81] In contrast to EG, HES involves other organs such as the heart, lungs, brain, and kidneys and generally has a progressive fatal course. [82] Eosinophilic granuloma (Langerhans cell histiocytosis), which can present as an antral mass, is diagnosed by its typical granulomatous appearance on biopsy. [83] An eosinophilic gastroenteritis, may precede or coincide with the vasculitic phase of the Churg-Strauss syndrome.[84]

Investigations

Peripheral blood eosinophilia is found in 20-80% of cases. [85] Average count is 2000 eosinophils (eos)/mL in patients with mucosal layer involvement, 1000 eos/mL in patients with muscular layer involvement, and 8000 eos/mL in patients with serosal involvement. The Erythrocyte Sedimentation Rate (ESR) can be elevated. Iron-deficiency anemia may be evident. Serum albumin may be low, especially in patients with mucosal layer involvement. [86] Protein loss can result in a low level of quantitative immunoglobulins. Serum IgE level can be elevated. Skin prick tests conducted to inhalant allergens and food help identify sensitization to specific allergens. [87]

Stool analysis for fecal protein loss can be measured by measuring alpha1-antitrypsin in a 24-h feces collection. This test is used to identify the inability to digest and absorb proteins in the GI tract. The normal value is 0-54 mg/dL. Patients with EG have elevated alpha1-antitrypsin in their feces. Three wet stool mount or stain smear are used to rule out parasitic infection. Mild-to-moderate steatorrhea is present in approximately 30% of patients. This can be measured by qualitative and quantitative stool tests. [88]

EG radiographic changes are variable. Gastric folds can be enlarged, with or without nodular filling defects. Valvulae conniventes may be thickened and flattened. Strictures, ulceration, or polypoid lesions may occur. In EG involving the muscle layer, localized involvement of the antrum and pylorus may occur, causing narrowing of the distal antrum and gastric retention. The small intestine also may be dilated, with an increase in the thickness of the folds. [89]

Ultrasound and CT scans may show thickened intestinal walls and, sometimes, localized lymphadenopathy. [90]

Endoscopy and biopsy specimens from the relevant sites is a good option to aid in diagnosis. The gross appearance of EG upon endoscopy shows erythematous, friable, nodular, and, often, ulcerated mucosa. It is preferable to obtain at least 6 biopsy specimens from normal and abnormal areas of the bowel. Grossly prominent mucosal folds, hyperemia, ulceration, or nodularity may be apparent. Histopathology usually demonstrates increased numbers of eosinophils (often >50 eos per high-power field) in the lamina propria. Large numbers of eosinophils often are present in the muscularis and serosal layers. [91] The localized eosinophilic infiltrates may cause crypt hyperplasia, epithelial cell necrosis, and villous atrophy. Diffuse enteritis with complete loss of villi, submucosal edema, infiltration of the GI wall, and fibrosis may be apparent. Mast cell infiltrates and hyperplastic mesenteric lymph nodes infiltrated with eosinophils may be present. Increased deposition of extracellular major basic proteins (MBPs) and Eosinophilic Cationic Proteins (ECPs) usually noted. Due to errors in sampling or to mucosal sparing, 10% of mucosal biopsies are not helpful for diagnosis. [92]

Ascitic fluid and pleural effusion usually are detected in patients with serosal layer involvement. Analysis of these effusions usually demonstrates a sterile fluid with a high eosinophil count. [93]

Laparoscopy may show hyperemia and/or nodularity of the GI wall. Sometimes exploratory laparotomy may be indicated, especially in patients with serosal EG. [94]

Treatment

Treatment is empiric and gauged to the severity of the clinical manifestations. [95] Spontaneous resolutions may occur. [96]

The response to elimination diets is generally poor, unless specific food(s) can be demonstrated reproducibly to precipitate symptoms. [97]

Patients with only mild diarrhea can be treated successfully with antidiarrheal medications, such as loperamide. [98]

Patients who are more symptomatic or have evidence of malabsorption need more aggressive therapy. Administration of prednisone (20 to 40 mg/day) is recommended. Improvement usually occurs within two weeks regardless of the layer of bowel involved. Prednisone should then be tapered rapidly over the next two weeks. However, some patients require more prolonged therapy (up to several months) to produce resolution of symptoms. Some patients have no recurrences, while a few experience recurrent symptoms during or immediately after the prednisone taper. The latter patients may require long-term, low-dose maintenance therapy with prednisone (eg, 5 to 10 mg/day). Other patients experience periodic flares months to years after the initial episode. They can be treated with another short course of oral prednisone, 20 to 40 mg/day, followed by a rapid taper. [99]

Mast cell stabilizers Disodium cromoglycate, Ketotifen, and oral cromolyn have been effective for short- and long-term management in some, but not all case reports. [100] Di- Sodium Cromoglycate (DSC) works by preventing mast cell degranulation, with a reduction in allergic inflammation. Allergic reactions involve an initial acute phase caused by vasoactive mediators, such as histamine, and a later inflammatory phase involving activation of lymphocytes and attraction of eosinophils. DSC prevents the allergic response and thereby prevents both early- and late-phase reactions. When disodium cromoglycate is effective, it would reduce inflammation and might act like corticosteroids. DSC is an alternative to corticosteroids; it can reduce the dose of corticosteroids in other patients. [101] Ketotifen (1-2 mg) is a mast cell and basophil stabilizer as well as an Histamine 1 receptor antagonist.

Sedation and drowsiness have been reported in a significant number of patients in clinical trials.[102] The leukotriene receptor antagonist, montelukast, may be useful as a steroid sparing agent in patients with the serosal form of eosinophilic gastroenteritis[(103)]. Eosinophils are potent sources of leukotrienes, including leukotriene C4 and leukotriene D4, molecules known to induce eosinophil chemotaxis, smooth muscle contraction, mucous secretion, and mucosal edema. Many factors may play a role in directing eosinophils to a site of inflammation. Cysteinyl-leukotrienes (CysLTs) are endogenous mediators of inflammation and play an important role in allergic disease by stimulating mucus production, mucosal oedema and inflammation, and dendritic cell maturation that prepares for future allergic response. Montelukast inhibits these actions by blocking type 1 CysLT receptors found on immunocytes, smooth muscle and endothelium in the intestinal mucosa. Montelukast has minimal side effects and are well-tolerated in most populations. [104]

A clinical response to antiallergic drug that suppresses cytokine production including IL-4 and IL-5 from Th2 cells; suplatast tosilate was described in clinical trials. [105]

Mycophenolate mofetil has been advocated but are generally not successful. After starting mycophenolate mofetil, patients on prednisone will be able to significantly decrease their mean daily dosage from 15 mg/d to 10 mg/d and may be able to discontinue prednisone use altogether. Mycophenolate mofetil (MMF) is a relatively well-tolerated immunosuppressive agent. MMF selectively and noncompetitively inhibits inosine monophosphate dehydrogenase in the *de novo* purine synthesis pathway. This enzyme facilitates the conversion of inosine monophosphate to xanthine monophosphate, an intermediate metabolite in the production of guanosine triphosphate. Because MMF results in the depletion of guanosine nucleotides, it impairs RNA, DNA, and protein synthesis. [106]

Alternative Chinese medicines are an option in treatment, but with limited data which needs further investigations. [107]

Finally; the accepted universal recommendation is to avoid surgery if at all possible, unless it is necessary to relieve persistent pyloric or small bowel obstruction. Reoccurrence is possible, even after surgical excision. [108] It is hoped that a better understanding of the pathogenesis and treatment of EG will emerge by combining holistic clinical and research approaches involving experts in the fields of allergy, gastroenterology, nutrition, and pathology. [109]

Prognosis

The natural history of Eosinophilic Gastroenteritis (EG) has not been well-documented. It is often chronic waxing and waning disorders. [110] Gastro-intestinal obstruction is the most common complication. Recurrent abdominal pain and intestinal perforation occur less frequently. [111] Untreated patients with EG can remit spontaneously or progress to severe malabsorption and malnutrition. Death from EG has been reported only rarely. Morbidity includes malnutrition and intestinal obstruction and perforation. Risk of cancer is not increasing. [112]

Eosinophilic Colitis

Eosinophils accumulate in the colons of patients with a variety of disorders, including eosinophilic gastroenteritis, allergic colitis of infancy, infections (including pinworms and dog hookworms), drug reactions, vasculitis (eg, Churg- Strauss syndrome), and IBD. Allergic colitis in infancy (also known as dietary protein–induced proctocolitis of infancy syndrome) is the most common cause of bloody stools in the first year of life. [113] Similar to other EGIDs, these disorders are classified into primary and secondary subtypes. The primary subtype includes the atopic and nonatopic variants, whereas the secondary subtype is divided into 2 groups, one composed of systemic eosinophilic disorders (HES) and the other composed of noneosinophilic disorders. [114]

Causes

In contrast to other EGIDs, eosinophilic colitis is usually a non-IgE–associated disease. Some studies point to a T lymphocyte–mediated process, but the exact immunologic mechanisms responsible for this condition have not been identified. In a murine model of oral antigen–induced diarrhea associated with colonic inflammation, colonic T cells have been shown to transfer the disease to naive mice through a STAT6-dependent mechanism. [115] It has been reported that allergic colitis of infancy might be an early expression of protein-induced enteropathy or protein-induced enterocolitis syndrome. Cow's milk and soy proteins are the foods most frequently implicated in allergic colitis of infancy, but other food proteins can also provoke the disease. Interestingly, this condition might more commonly occur in infants exclusively breast-fed and can even occur in infants fed with protein hydrolysate formulas. [116]

Clinical picture and diagnosis

Similar to eosinophilic gastroenteritis, there are a variety of symptoms associated with eosinophilic colitis, depending on the degree and location of tissue involvement. Although diarrhea is a classic symptom, symptoms that can occur independent of diarrhea commonly include abdominal pain, weight loss, and anorexia. There is a bimodal age distribution given the infantile form presented at a mean age at diagnosis of approximately 60 days and the other group presenting during adolescence and early adulthood. In infants, bloody diarrhea precedes diagnosis by several weeks, and anemia caused by blood loss is not uncommon. The majority of infants affected do not have constitutional symptoms and are otherwise healthy.[117] On endoscopic examination, patchy erythema, loss of vascularity, and lymphonodular hyperplasia are seen mostly localized to the rectum but might extend to the entire colon. Histologic examination often reveals that the overall architecture of the mucosa is well preserved, but there are focal aggregates of eosinophils in the lamina propria, crypt epithelium, and muscularis mucosa and, occasionally, the presence of multinucleated giant cells in the submucosa. No single test is the golden standard for diagnosis, but peripheral blood eosinophilia or eosinophils in the stool are suggestive of eosinophilic colitis. [118]

Treatment

Treatment of eosinophilic colitis varies, primarily depending on the disease subtype. For example, eosinophilic colitis of infancy is generally a benign disease. On withdrawal of the offending protein trigger in the diet, the gross blood in the stools usually resolves within 72 hours, but occult blood loss might persist longer. [119] Treatment of eosinophilic colitis in older individuals usually requires medical management because IgE-associated triggers are rarely identified. Drugs, such as cromoglycate, montelukast, and histamine receptor antagonists, are generally not successful in some author's experience. Anti-inflammatory drugs, including aminosalicylates and glucocorticoids (systemic or topical steroids), are commonly used and appear to be efficacious, but careful clinical trials have not been conducted. There are several forms of topical glucocorticoids designed to deliver drugs to the distal colon and rectum, but eosinophilic colitis typically also involves the proximal colon. In severe cases, refractory or dependent on systemic glucocorticoid therapy, intravenous alimentation or immunosuppressive antimetabolite therapy (azathioprine or 6-mercaptopurine) are alternatives. [120]

Prognosis

When eosinophilic colitis presents in the first year of life, the prognosis is very good, with the vast majority of patients being able to tolerate the culprit food or foods by 1 to 3 years of age. Several studies have found an association between allergic colitis and later development of IBD, but this association is controversial. The prognosis for eosinophilic colitis when it develops later in life is more guarded than the infantile subtype. Similar to eosinophilic gastroenteritis, the natural history has not been documented, and this disease is considered to be

a chronic waxing and waning disorder. Because eosinophilic colitis can often be a manifestation of other primary disease processes, routine surveillance of the cardiopulmonary systems and regular upper and lower gastrointestinal endoscopy is recommended. [121]

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الاضطرابات المعوية الحمضية

كساب الحرفوشي

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الملخص

تعد الاضطرابات المعدية الحمضية أمراضاً التهابيةً نادرةً من نوعها، حيث لم يعرف أصلها وسببها بعد. تعرف هذه الاضطرابات على أنها تؤثر على القناة المعدية بطريقة غير عشوائية مسببة التهاباً حمضياً بالرغم من عدم وجود أسباب معروفة وظاهرة لزيادة الحموضة منه (مثل التهيجات الناتجة عن تناول الأدوية أو عدوى طفيلية، أو وجود الأورام الخبيثة).

يتذبذب ويتفاوت مستوى الأحماض عند المريض بهذا النوع من الاضطرابات بحيث يسبق بكثير وقت ظهور الأعراض عليه، أو انها قد تكون في انخفاض وقت التشخيص، مما يضلل الطبيب ويصعب عليه عملية التشخيص.

تم اقتراح آلية التحسس كمسبب عند مجموعة من المرضى على الأقل.

في الحقيقة، تم التعرف على وجود مستويات مرتفعة من (IgE) الإجمالي و (IgE) الناتج من الطعام في معظم المرضى الذين وجدت لديهم هذه الاضطرابات. كما كانت استجابات معظم المرضى لاختبارات الجلد إيجابيةً بالنسبة لمولدات الضد في مجموعة من الأطعمة، ولكنهم لم يولدوا ردود أفعال استهدافية نمطية، مما يعتبر مشابهاً لنوع متأخر من متلازمة الحساسية المفرطة للطعام.

تغلب نسبة الذكور الذين يصابون بهذه الاضطرابات على نسبة الإناث وخاصة أولئك من الفئة العمرية (30-50) عاماً. (27%) من المصابين لديهم تاريخ بالإصابة بمرض الاستشراء. قد تتفاوت ظهور الأعراض على المريض، فقد تصيب عضواً واحداً فقط بالارتشاح الحمضي وقد يصيب أجهزة جسدية بأكملها.

من أكثر الأعضاء تأثراً بهذه الاضطرابات التجويف المعوي والأمعاء الدقيقة، التي غالباً ما تظهر عليها أعراض الانسداد.

من الأعراض النادرة (تقرح فرانك)، والنزف الدموي. ومن الأعراض غير الملازمة الغثيان والتقيؤ وعسر الهضم وحدوث آلام في البطن ونقصان الوزن. (80%) تقريباً من المصابين تظهر عليهم الأعراض لسنوات عدة قبل تشخيص المرض واكتشافه، ويمكن أن تظهر هذه الاضطرابات المعوية على شكل اعتلال معوي مع نقص بالبروتين. يعد الالتهاب المصلي أحد أكثر الأسباب المحتملة للحبن النضحي. أما الانسداد الصفراوي فهو يعد من الأشكال النادرة لظهور هذه الاضطرابات، ويمكن أن يخطئ الطبيب في تشخيص هذه الاضطرابات ويظنها ورماً بالخطأ.

يمكن أن تبين الصور فوق السمعية أو التصوير القطاعي المحوسب أو دراسات التباين خصائص وميزات غير محدودة لجدار الأمعاء والغشاء المخاطي المتضخم. من الأعضاء النسجية المميزة خزب الاستسقاء المخاطي، والارتشاح الحمضي الكثيف، وضخامة حزمة العضلات، والتليف.

يعد الغشاء المخاطي المتفرع من أكثر الأنسجة المتأثرة وقد يحتاج الطبيب الى خزعات تامة الكثافة من أجل التشخيص.

غالباً ما يكون العلاج غير مُرضٍ، حيث تكون النتائج بعيدة المدى غير أكيدة، ويبقى العلاج باستخدام (Prednisolone) بجرعة (20-40) مغ يومياً علاجاً تجريبياً. يمكن أن تكون العلاجات باستخدام حميات الاطّراح وكروموجلايات الصوديوم ناجحة في حالات نادرة عندما يكون مولد الضد المسبب للاضطراب قد تم عزله.

أيد العديدون بعض الأدوية مثل:montelukast ، ketotifen، suplatast tosilate، mycophenolate mofetil وبعض الأدوية الصينية البديلة ولكنها غالباً ما تكون غير ناجحة وقد تحدث الانحلالات العفوية غير المتوقعة.

نأمل أن نصل الى فهم أعمق حول أمراض ومعالجة هذا النوع من الاضطرابات عن طريق دمج المدخل السريري العلاجي والمدخل البحثي معاً بالاشتراك مع مختصين في مجال التحسسية، وعلم الجهاز الهضمي والتغذية وعلم الأمراض.

الكلمات الدالة: الاضطرابات الهضمية الحمضية، مثبتات الخلايا البدينة، مضادات مستقبلات ليوكرتين.