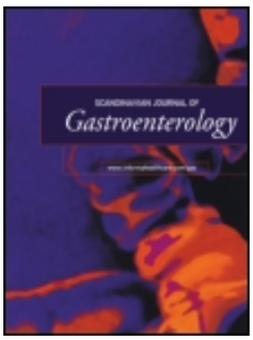

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Alfredo J. Lucendo

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REVIEW ARTICLE

Eosinophilic diseases of the gastrointestinal tract

ALFREDO J. LUCENDO

Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, (Ciudad Real), Spain

Abstract

Eosinophilic gastrointestinal disorders (EGIDs) are a diverse group of disorders whose diagnosis is on the rise and are characterized by symptoms caused by infiltration by eosinophils of the different sections of the digestive tract. Although little is known of their etiology, it seems to be multifactorial. Alteration of the immunological capacity of the digestive mucosa is determined by the exposure of genetically predisposed individuals to potential airborne or food allergens. EGIDs are classified based on the location of the inflammatory response even though their symptoms, prognosis, and treatment vary considerably. Eosinophilic esophagitis is the most widely recognized entity in this family and is characterized by exclusive eosinophilic infiltration of the esophagus. Breakthroughs in understanding its etiopathogeny have been extrapolated to eosinophilic gastroenteritis, a rare disease identified many years ago commonly involving the stomach and small bowel which should be distinguished from hypereosinophilic syndrome. Eosinophilic colitis, which usually affects children, could be considered a specific non-IgE-mediated allergy to food protein. The physiopathological bases of these entities need to be established in order to define specific treatment aimed at preventing and altering their clinical evolution.

Key Words: *Eosinophils, eosinophilic colitis, eosinophilic esophagitis, eosinophilic gastroenteritis, hypereosinophilic syndrome*

Introduction

Eosinophils are granulocytes which come from the bone marrow and have pro-inflammatory functions involved mainly in protecting against parasites [1] and allergies [2,3]. The biology of these functionally complex cells is still not entirely known, but they are currently considered multifunctional. Eosinophils can cause tissue damage through the preformed cytotoxic proteins in their cytoplasmatic granules [4], they release inflammatory mediators which activate the endothelium and, on their own can stimulate T-lymphocytes and provoke antigen-specific immune responses *in vivo* by acting as antigen-presenting cells [5]. Eosinophils are recruited from the blood towards the tissues, including the digestive tract, where they perform their functions. They are part of the normal structure of certain digestive tract organs where they are more numerous than in other tissues, although under normal conditions they do not infiltrate the epithelium. Eosinophils are concentrated mainly in the small intestine and the right colon and are not usually present in the esophagus. The excessive accumulation of eosinophils in tissues and their presence in the epithelium [5] is a common finding in numerous gastrointestinal disorders including IgE-mediated food allergies, eosinophilic gastrointestinal disorders (EGIDs) [6], gastroesophageal reflux [7,8], and inflammatory bowel disease [9–11], where they could be responsible for wrong prognosis [12,13]. Although there is no fixed number of eosinophils that can be used as a cut-off criterion to define disease [14], in each of these processes, the pro-inflammatory functions of eosinophils contribute to tissue damage.

EGIDs are a group of inflammatory diseases of unknown origin, whose common histological characteristic is dense infiltration by eosinophilic leukocytes affecting different layers and sections of the digestive tract without any known causes of eosinophilia [6], such as parasitic infections, reactions to medication or

Correspondence: Alfredo J. Lucendo, MD, PhD, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n. 13700 Tomelloso, (Ciudad Real), Spain. Tel: +34 926 525 927. Fax: +34 926 525 870. E-mail: alucendo@vodafone.es

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neoplasias. Although they have been known of for many years, Eosinophilic Gastroenteritis (EG) was first described by Kaijser in 1937 [15], these pathologies have recently gained importance as a result of information acquired in relation to their physiopathology. Eosinophilic esophagitis, (EoE), which has gained recognition in recent years (the most frequent type of eosinophilic gastroenteropathy), has rekindled interest in these inflammatory diseases. Their epidemiology could be on the rise, which poses a significant diagnostic and therapeutic challenge.

Gastrointestinal eosinophilic diseases may be classified based on the affected topography of the digestive tract. Thus, EoE is characterized as exclusively affecting this organ. Eosinophilic gastroenteritis involves infiltration by eosinophils of the stomach and duodenum, possibly involving the esophagus or colon in certain cases. Eosinophilic proctocolitis, caused by proteins in the diet, has characteristic clinical and epidemiological manifestations. Hypereosinophilic syndromes (HES) are a group of systemic diseases which can also affect the digestive tract in certain cases. Although these diseases have various aspects in common, their epidemiological characteristics, clinical evolution, prognosis, and treatment can vary radically.

Epidemiology

EGIDs were considered to be very rare and have been particularly identified in atopic patients. They have only recently caught the attention of gastroenterologists and the wide recognition of EoE in all developed countries has sparked new interest in this type of pathology and in identifying new patients with symptoms dependent on the localization and intensity of the inflammatory response (abdominal pain, failure to thrive, irritability, vomiting, diarrhea, bowel dysmotility, or dysphagia) and endoscopic and histological exploration.

However, we have 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. The density of the eosinophilic infiltrate or its precise location in the wall of the organs of the digestive tract has not been consensually defined and these aspects may vary widely as shown by variations in different geographical areas [16]. Considering all of the above, we could say that over the past few decades we have witnessed a sharp rise in the prevalence of EGIDs, as evidenced by the rapid growth in reported cases of EoE in numerous populations. Over the past 10 years there has been an 18-fold rise in the prevalence of EoE in Australia [17] and a 35-fold rise in Philadelphia [18].

The hygiene hypothesis [19] provides a general explanation for the increase in EGIDs and allergic diseases parallel to a decrease in infectious diseases. Overly hygienic environments (from controlling exposure to microorganisms during childhood) have led to changes in the patterns of gut microflora and a decrease in exposure to helminths, causing an imbalance of the immune system and a tendency to develop allergic and autoimmune disorders [20]. A change in the fine tuning of T helper cell 1 (Th1), Th2 and regulatory T cell responses which are triggered by altered or missing innate immune cell activation could be responsible for this phenomenon. In fact, the influence of Th2 cells, which are important in the development of IgE responses and eosinophilia, normally wanes over the first two years of life in nonallergic individuals, possibly secondary to Th1 stimulation caused by bacterial infection [16].

A population-based study conducted in Sweden estimated that esophageal eosinophilia were present in about 1% of the adult population [21]. Although more correctly diagnosed cases of EoE would also contribute to its rising prevalence, its increase, parallel to that of bronchial asthma in common geographical areas, is proof of its rising epidemiology.

Pathophysiology

In terms of their physiopathological mechanisms, EGIDs are considered mixed disorders, some of which have IgE-mediated characteristics (such as oral allergy syndrome or anaphylactic reactions triggered by food) and others which are exclusively cell-mediated (food protein-induced colitis or celiac disease). EGIDs seem to be caused by both environmental and genetic factors. The fact that approximately three out of four patients are atopic reinforces the idea that the accumulation of eosinophils in the digestive tract is caused by the exposure of patients to dietary [22,23] or airborne antigens [24]. What is more, the severity of the disease can occasionally be reversed using allergen-free diets [18,25]. These data show that immunoallergic disorders are the physiopathological source of most eosinophilic gastroenteropathies, although in a few cases, the patients failed to show antigenic sensitivity following the appropriate studies.

The high frequency of these diseases in members of the same family (10% of patients have other family members with EGIDs [6,26]) suggests that certain immune response regulatory genes play a role in the

origin of the disease. There has been recent speculation on the possible involvement of gastroesophageal reflux specifically in the physiopathology of EoE [27], although the co-existence of both processes could be considered as both the cause and effect [28]. In this respect, eosinophilic gastroenteropathies could either have a multifactorial cause determined by the exposure of the digestive mucosa of the immune system to food or airborne allergens, modulated in certain cases by the exposure of genetically predisposed individuals to acid. The contribution of these possible etiological factors to the development of these various diseases is crucial to define specific treatment.

Research on the molecular pathogenesis of EGIDs was based on different strategies. The highly acknowledged incidence of EoE allowed research to be extrapolated to other types of digestive eosinophilia. Eosinophil recruitment towards the wall of the digestive tract follows the stimuli which modulate the biology of these cells, and this knowledge is acquired from studying allergic diseases, especially bronchial asthma. Animal models of EoE have shown that the disease is driven by Th2 cytokine pathways known to be associated with allergic disorders, in which interleukine (IL)-5 and IL-13 seem to be important mediators [29,30]. Eotaxins are a group of chemokines which have chemotactic effects on eosinophils and act upon the C-C receptor-3 (CCR3) chemokine receptors. Research examining the gene expression profile of the esophageal tissue of EoE patients showed an increased expression of eotaxin-3 mRNA compared to normal controls [31]. Eotaxin-3 is the most highly upregulated gene in the EoE genome and seems to be mainly expressed by the epithelial cells of the esophagus. A single nucleotide polymorphism in the eotaxin-3 gene has been associated with increased susceptibility to EoE [31]. Other molecules such as eotaxin-1 could also help eotaxin-3 recruit eosinophils towards the esophagus in EoE, whereas eotaxin-1 mRNA is also upregulated in EoE patients [32] and this chemokine has a considerably higher affinity for CCR3 than eotaxin-3. Murine models of EG have shown that gastrointestinal eosinophilic inflammation induced by oral antigen challenge is dependent on eotaxin-1 [33].

Stricture formation is a serious complication in EGIDs. Fibrous remodeling of the subepithelial layers of the esophagus has been observed in children affected by EoE, like in bronchial asthma. IL-5, transforming growth factor beta - β and its signaling molecule phosphorylated SMAD2/3 have been considered responsible for esophageal remodeling, as well as in asthma [34].

Therapeutic tools have been recently developed aimed at cytokines causing the inappropriate accumulation of eosinophils in the gastrointestinal (GI) tract using mepolizumAb, an anti-IL-5 monoclonal antibody which could lead to promising new therapies for EGIDs.

Eosinophilic esophagitis

During the 1980s, eosinophilic inflammation of the esophagus was considered a pathognomonic histopathological sign of gastroesophageal reflux disease [7,35]. However, the therapies based on controlling exposure to acid were inefficient in treating many patients, mainly children with dysphagia and other esophageal symptoms linked to this inflammation [36]. The resolution of esophageal eosinophilia using elemental diets (based on amino acids and lacking in antigenic capacity) proved that this disease had an underlying allergic mechanism [37], which also became well-characterized in adults as a clinicopathological syndrome [38]. In recent years, the epidemiology of the disease has undergone an explosion. The cases reported in literature mainly hail from Europe and the US and to a lesser extent, from Asia, Latin America, and Australia. Its distribution across all continents, except Africa, is parallel to bronchial asthma and other atopic diseases which affect the most socio-economically developed geographical areas. This suggests that their etiopathogeny has environmental and immunological factors in common with other allergic forms of the disease, whose principles have also been extrapolated to other EGIDs.

Over 65% of EoE cases manifest during childhood [39], although it has been described in patients of all ages [40]. Unlike other immunoallergic diseases, EoE predominantly affects males in all age groups (over 75%) and most commonly appears in adults in their thirties and fifties [41]. Most cases described affected Caucasians, were less frequent in Asians [42] and were particularly rare in blacks.

Eosinophilic inflammation in EoE restricts the esophagus and does not affect the more distal sections of the digestive tract. While the human esophagus is completely eosinophil-free under normal conditions, EoE is the clearest expression of EGIDs. The characteristic manifestations of dysphagia vary in different age groups, probably depending on whether or not patients are capable of correctly communicating their symptoms; small children tend to refuse food, have vomiting, or abdominal pain [43] and from adolescence onwards, dysphagia and food impactation are the symptoms which most clearly lead to diagnosis [44]. Recognition of the symptomatology, together with other various histopathological findings (such as eosinophilic degranulation [45], proliferative changes in the epithelium or the formation of eosinophilic microabscesses [46]) have led to a reduction in the number of eosinophils required for diagnosis to

15 per high power field (HPF) which is currently accepted [47].

Eosinophilic gastroenteritis

EG involves tissue eosinophilia of any layer or layers of the gut wall, stomach or small intestine and determines gastrointestinal symptoms without parasitic infection. Even today it is considered rare and has not increased to the same extent as EoE. Unlike EoE, EG does not predominantly affect people of any particular gender or race and although it can affect any age group, most cases relate to adults between their thirties and fifties [22] and are detected by endoscopic exploration and biopsies of the mucosa performed as a result of abdominal pain or diarrhea [48].

From a clinical viewpoint, EG manifests itself differently depending on how deep the eosinophilic infiltrate affects the wall of the organ. Clinical features may reflect the extent, location, and depth of infiltration of this eosinophilic inflammatory process in the GI tract [49]. The most common form is characterized by mucosal and submucosal infiltration, whose symptoms include abdominal pain, diarrhea, weight loss, and other manifestations related to malabsorption, such as iron deficiency, blood loss, and protein-losing enteropathy [48]. In other forms, pathologic inflammation can penetrate deeply into the muscle layer, causing a thickening of the bowel wall, which might typically result in symptoms of obstruction. Although any part of the GI tract can be affected, the stomach and duodenum are most commonly involved [50].

The rarest form of EG is serosal disease in which eosinophil-rich inflammation affects all the layers of the bowel wall, determining eosinophilic ascites.

Various aspects of EG are noteworthy: peripheral eosinophilia is common in EG and is found in up to 80% of patients. It is more intensive in patients with mucosal or serosal forms and ascites than in those with muscular affectation [49]; a history of atopia is common with regard to the mucosal and serosal forms of the disease and does not tend to occur in muscular forms [22]. Fifty percent of patients with EG also have esophageal involvement. EG is a severe disease with heterogeneous clinical manifestation. In some patients, the condition can resolve itself permanently over time, but it is more likely to be characterized by recurrent relapses [16]. In some pediatric patients [51], the disease manifested under the age of 1 year and was resolved by excluding milk from the diet. When EG appeared later in childhood, it was associated with IgE-mediated hypersensitivity reactions to food and did not respond to dietary changes. Some adult patients affected by muscular-type EG were cured from the disease after the affected segment was surgically removed [50].

This data shows that there could be a combination of different phenotypes involved in EG and considerable differences among the underlying mechanisms causing eosinophilic inflammation. It might be useful to develop a world-wide registry of well-characterized patients in order to improve our knowledge of its epidemiological and clinical features [16].

Eosinophilic colitis

The tissue density of eosinophils in the colon increases under numerous pathological circumstances including infection and parasitosis, reactions to medication, vasculitis, following radiotherapy treatment [52] and inflammatory bowel disease. Eosinophils were frequently observed in colon biopsies from patients with ulcerative colitis, and although they only represented a small proportion of the inflammatory infiltrate cells [9], their activation and the secretion of cytotoxic granular proteins correlated with the morphological changes and the clinical severity and level of GI dysfunction [53,54]. However, eosinophilic colitis is the most characteristic clinical type of eosinophilic infiltration of the colon. It includes two different well-characterized syndromes, as follows:

Allergic eosinophilic proctocolitis (AEPC)

Discovered in 1940 [55], AEPC is an inflammatory reaction of the colon and rectum which responds to an immune reaction triggered by the intake of foreign proteins [56]. Cows' milk proteins are involved in almost every case although other foods have also been associated. Around 60% of cases relate to breast-fed children, the allergen in this case being cows' milk proteins consumed by the mother (especially β-lactoglobulin), which is excreted with breast milk [57].

Clinical manifestations appear in unweaned babies generally between 2 days and 3 months old in the form of bloody-mucous diarrhea deposits which tend to persist until the causal agent is removed, without affecting the general welfare of the unweaned baby or reducing its weight gain. Analytical alterations are not usually found and allergic skin tests and specific IgE are negative. Rectosigmoidoscopies and biopsies lead to diagnosis in cases which do not respond to the removal of the protein. Affectation of the colon tends to be patchy, with areas of edematous mucosa and possible superficial erosions or ulcers. In rectal biopsies,

there is infiltration by more than 20 eosinophils/HPF in the thickness of the mucosa and *lamina propria* [58].

Food protein-induced enterocolitis (FPIE)

FPIE appears within the first six-months of life and involves diarrhea and vomiting of variable severity affecting infants several hours after certain food proteins are ingested [59]. It is more severe than AEPC insofar as it can lead to dehydration, lethargy, and shock, including malnutrition and stunted growth. Both the small and large intestines are usually affected and the involvement of the latter can determine the appearance of blood in the feces in the latter.

Cows' milk is most frequently involved food and symptoms appear when it is used to substitute breast milk which acts as a protective factor (no cases have been described in children fed in this manner). Symptoms appear gradually and can also be triggered by other foods such as soya protein, eggs, pulse vegetables, and cereals [56], and sometimes by various foods simultaneously.

Although most patients with FPIE are infants reactive to milk and/or soya, this diagnosis should be considered in older children for other foods. Children up to 2 or 3 years old tend to develop a tolerance to the food causing the symptomatology but some patients may develop food-specific IgE sensitivity.

Hypereosinophilic syndrome

HES are a heterogeneous group of rare systemic diseases of idiopathic origin, characterized by marked blood eosinophilia (at least 1500 cells/mm^3) persisting for more than 6 months. There can be found signs or symptoms of organic affectation [60] with eosinophils in the GI tract.

First described in 1968 [61], HESs predominantly affect males between 20 and 50 years old [62]. HES patients traditionally develop eosinophilic endocardial disease with embolization of peripheral organs such as the extremities and the brain [6]. Patients show high levels of mast cell tryptase in serum [63] and bone marrow analyzes show a high number of dysplastic mast cells which decrease after treatment with the tyrosine kinase inhibitor Imatinib Mesylate [64,65]. Consequently, HES could be related in some way to systemic mastocytosis and chronic myelogenous leukemia.

As per the definition, patients with EGIDs and sustained blood eosinophilia exceeding 1500 cells/mm^3 would have HES. Therefore, routine surveillance of the cardiorespiratory system is warranted, especially if the patients have extragastrointestinal manifestations.

Treatment of EGIDs

The heterogeneity of the different diseases in this group has led to different treatment strategies, including controlling exposure to food allergens and various drugs with efficient anti-inflammatory action in different allergic pathologies. However, so far, no medication for EGIDs has been specifically approved by regulatory agencies in either the US or the European Union which is a major obstacle in caring for these patients [66]. Most research on EGID treatment has been carried out in relation to EoE. However, only two randomized studies are currently available which assess the efficiency of interventions [67,68] and there is no universally accepted consensus for the management of EoE [69]. Conversely, due to the clinical characteristics and topographical localization of EoE, it is difficult to extrapolate its treatment results to other EGIDs. Nevertheless, available data could provide guidance for developing new research strategies.

Treatment of EGIDs by controlling exposure to dietary allergens

In view of the close relationship between food allergies and many EGIDs, one of the most widely tested strategies in treating the various types of EGIDs was based on controlling antigen exposure in the diet. In EoE, considerable effort has been made in testing the efficiency of the diet to cure symptoms, especially in pediatric patients. Elemental diets, which are exclusively based on amino acids, are highly efficient [18,37] but impractical in the long term. Therefore, other options have been used, such as eliminating foods which provoke a hypersensitivity reaction. The combination of prick and patch tests [25] resolved the symptoms in over half the cases, but it was impossible to identify which food was responsible in some cases. Because these tests are not particularly successful in detecting allergies, cutting out foods which were potentially more allergenic regardless of the result of the allergy tests (six different foods including cows' milk protein, soya, wheat, eggs, peanuts, and seafood), resolved the symptoms in 74% of the children studied [70], while a lower success rate was achieved in adults [71].

In EG, complete resolution of the eosinophilic infiltrate is generally achieved using amino acid-based elemental diets, while cutting out the food in question through skin prick testing (or radioallergosorbent test) has variable effects [6,72]. Once the disease is in remission, the specific food groups should be slowly and gradually reintroduced until those causing allergies have been identified when symptoms reappear.

Eosinophilic colitis or milk-protein colitis usually disappears once the offending protein has been removed from the infant's diet, either if the breastfeeding mother follows an elimination diet, or by trial using a hydrolysate or an amino acid-based formula [23].

Anti-inflammatory drugs in EGID treatment

Several studies have analyzed the usefulness of systemic steroids in EoE. This therapy has proven highly efficient in restoring normal esophageal histology and providing symptomatic relief, but relapse was common once the steroid was withdrawn. Topical steroids were then used in order to avoid the side-effects of systemic steroids over long-term use. Fluticasone propionate was the most widely used drug due to its efficiency, which was similar to prednisone [73] and better than a placebo [68]. Its safety profile qualifies fluticasone propionate for treating children and adults with this disease. It is sprayed onto the tongue and then swallowed [46]. A viscous budesonide solution was helpful to children who were unable to puff and swallow and there were no changes in the patient's morning cortisol levels [74].

Anti-inflammatory steroid drugs have been widely used to treat EG. This is the main therapy used for patients for whom dietary restrictions are not feasible or if there has been no improvement [6], especially budesonide which acts mainly on the distal small bowel and colon. Steroid-dependent or steroid-refractory patients may be treated with thiopurines (azathioprine or 6-mercaptopurine), a strategy also assessed in EoE [75].

Anti-allergic drugs in EGIDs

Regarding the benefits of other anti-allergic drugs in EG, unfortunately, most information available comes from case reports based on a small number of patients. Therefore, we do not have enough evidence to guarantee how useful these drugs are. The mast cell stabilizer disodium cromoglycate was inefficient in pediatric patients with EoE [18], but some patients with EG obtained certain benefits from this drug [76,77]. Ketotifen and H1-antihistamines succeeded in reducing tissue eosinophilia and its symptoms in patients with EG [78,79] as did suplatast tosilate in the only patient treated for EG [80].

High doses of the leukotriene antagonist montelukast were used in a small group of adult EoE patients surveyed by telephone, most of whom reported symptomatic improvement, but they had persistent esophageal inflammation [81]. In several other EG case reports, montelukast did not provide any benefits [82–84].

Results of biological treatment for EGIDs

MepolizumAb, an anti-IL-5 monoclonal antibody, was initially used for HES resulting in corticosteroid sparing [85], but led to rebound eosinophilia after treatment [86]. After a promising effect on four EoE patients [87], a multicenter double-blind placebo-controlled assay evaluated the efficiency of mepolizumAb to treat severe EoE in adult patients: Used in monotherapy it significantly reduced eosinophil density in esophageal tissues by approximately 50%, but the eosinophils did not decrease any further once the dosage was increased. Minimal clinical improvement was achieved in a subgroup of EoE patients [88]. OmalizumAb, a specific anti-IgE monoclonal antibody which increases the concentration of allergens required to trigger an allergic response, seemed not to be effective in reducing tissue eosinophils in the treatment of EoE patients [89,90], even when peripheral blood eosinophils had decreased. The anti-TNFα antibody InfliximAb had no beneficial effect on the inflammation or symptoms of EoE in adult patients [91].

Endoscopic treatment in EoE

In EoE the esophageal mucosa is extremely fragile. A high number of mucosal tears and lacerations have been described, secondary to both the patients' efforts to induce vomiting and dislodge the impacted food and after endoscopic dilation. Chronically maintained esophageal inflammation itself seems to alter the elasticity and resistance of the layers of the wall of the esophagus. Cases of spontaneous esophageal perforation [92] and Boherhaave's syndrome [93] have also been reported after the endoscope was introduced [94] in patients with EoE, which means that endoscopic procedures need to be performed more gently. Alterations in the caliber of the esophagus and a narrowing of the lumen frequently observed in EoE have led to the use of mechanical dilation as a treatment option, like in other cases of rigid or fibrous stenosis. Literature shows that esophageal dilation is an efficient treatment method providing immediate symptomatic relief [95,96], although there is a greater risk of complications in EoE [97]. It has been suggested that the long evolution of dysphagia, the existence of esophageal stenosis and the high density of eosinophils are predictive factors of these complications during dilation [98]. Mechanical dilation has no effect on the underlying inflammatory process and has limited efficiency in EoE over time and patients are required to undergo repeated dilations [99,100] to control their symptoms. Because mechanical dilation is a risky technique for EoE patients [97], endoscopic dilation should be considered as a treatment

alternative only for patients with EoE and esophageal stenosis once other measures have failed, especially dietary modification and topical steroids [100].

Conclusions

EGIDs are a diverse group of pathologies which are becoming diagnosed more frequently and have been traditionally classified according to the localization of the infiltration by eosinophils and their symptoms. However, a new global approach is required in the study of these diseases which could include common underlying physiopathological mechanisms. The complete documentation of cases analyzing the clinical, immunological, and histopathological characteristics of patients could act as a basis for multicentric ulterior studies defining the etiology, pathogenesis and best treatment alternatives to prevent and modify the development of these exciting pathologies.

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