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Idiopathic eosinophilic gastrointestinal diseases in adults

Alex Straumann* MD

Associate Professor

Department of Gastroenterology, Kantonsspital Olten, Olten, Switzerland

This review focuses on the latest cognitions, diagnosis and treatment strategies of the three main representatives of the eosinophilic gastrointestinal disorders (EGID): idiopathic *eosinophilic oesophagitis* (EE), idiopathic *eosinophilic gastroenteritis* (EGE) and idiopathic *hypereosinophilic syndromes* (HES) with gastrointestinal involvement. These disorders share important similarities: their origin is unknown and their pathogenesis is due to a histological inflammatory response characterised by eosinophilic tissue infiltration.

In spite of these parallels, the courses and prognoses of the diseases differ radically: EE is restricted to the oesophagus, and though it may significantly decrease the patient's quality of life, it has a favourable long-term prognosis. In EGE, the inflammatory process involves several segments of the gastrointestinal tract but this chronic inflammation may also be considered a benign disorder. In contrast, HES is primarily a multisystem disorder that may involve several organs, including the digestive tract, and often has a fatal outcome.

Key words: eosinophilic gastrointestinal disorders; eosinophilic oesophagitis; eosinophilic gastroenteritis; hypereosinophilic syndrome.

INTRODUCTION

The adjective, 'idiopathic', stems from two Greek roots, *idio* (reflexive or pertaining to itself) and *pathy* (suffering or disease), and is used to classify diseases in which the mechanisms or origin of a condition is obscure or unknown. The idiopathic disease may comprise several different entities. The term, 'eosinophilic', denotes that the

Abbreviations: ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EE, eosinophilic oesophagitis; EGE, eosinophilic gastroenteritis; EGID, eosinophilic gastrointestinal disorder; GERD, gastro-oesophageal reflux disease; HES, hypereosinophilic syndromes; HPF, high power field.

* Corresponding author: Roemerstrasse 7, 4600 Olten, Switzerland. Tel.: +41 62 212 55 77; Fax: +41 62 212 55 64.

E-mail address: alex.straumann@hin.ch

histological inflammatory response is predominantly characterised by an eosinophilic tissue infiltration. Moreover, it is likely that eosinophils play a pivotal role in the pathogenesis of these disorders. Recent practice classifies those idiopathic eosinophilic infiltrations that occur primarily in the gastrointestinal tract under the umbrella acronym of eosinophilic gastrointestinal disorder(s) (EGID).¹

In this review, we focus on the three main representatives of the EGID, in particular, on idiopathic *eosinophilic oesophagitis* (EE), idiopathic *eosinophilic gastroenteritis* (EGE) and idiopathic *hypereosinophilic syndromes* (HES) with gastrointestinal involvement. Because each of these conditions has different properties and likely its own pathogenesis, to subsume them into one single category is quite arbitrary and based exclusively on descriptive features. EE is definitely an oesophageal-restricted disease with a favourable long-term prognosis.² In patients with EGE, the inflammatory process involves several segments of the gastrointestinal tract but, nevertheless, this chronic inflammation can also be considered a benign disorder. In contrast, HES is primarily a multisystem disorder that may involve several organs, including the digestive tract, and often has a fatal outcome.^{3,4} Despite these fundamental differences, all three conditions share the same features of being 'idiopathic' and 'eosinophilic', and, as long as our understanding of the underlying mechanisms remains so fragmentary, we may take the liberty of classifying them into one single category.

EOSINOPHILIC OESOPHAGITIS

Eosinophilic oesophagitis (EE) is by far the most common EGID. Because of its clinical relevance, EE is discussed here in more depth than are the other EGIDs.

Definition

Considering that the first comprehensive descriptions of this inflammatory oesophageal disease were published in the early 1990s, not quite 15 years ago, EE can be viewed as a relatively young disorder.⁵⁻⁷ Nevertheless, in this short time, EE has become an acknowledged and well-recognised disease. However, as the presenting symptoms may mimic those of gastro-oesophageal reflux disease (GERD), defining EE is not always straightforward. Moreover, oesophageal eosinophilia is not found uniquely in EE and the endoscopic features of EE are often uncharacteristic or confusing. The following paraphrase, based on clinical and pathological features, has proven feasible for clinical as well as for research purposes: EE is characterised by oesophagus-related symptoms in combination with a dense oesophageal eosinophilia, both of which persist despite prolonged treatment with proton pump inhibitors.⁸

Epidemiology

During the last few years, gastroenterologists in industrialised countries all over the world have experienced a dramatic increase in the number of diagnosed EE cases.⁹⁻¹³ Interestingly, so far no patients have been reported from developing countries or from tropical areas. EE seems to be a typical disease of civilisation. There is a huge body of evidence suggesting that EE's prevalence is increasing at a startling rate, but there is still an on-going debate about how common this disorder actually is. Recent data from a population-based longitudinal study showed that throughout the observation period lasting more than a decade and a half, EE has an average annual incidence of

1.88 newly diagnosed cases per 100 000 inhabitants, with a marked increase in newly-diagnosed cases during recent years. Thus, the current cumulative prevalence is 32 affected individuals per 100 000 inhabitants.¹⁴ Given the lack of mortality associated with EE, the prevalence over time will increase even if the incidence remains stable. Of note, because the area examined was geographically stable and recording practices were consistent, it is unlikely that this increase can be entirely accounted for by increased recognition. Summarising, it is likely that EE is one of today's leading causes of dysphagia and food impaction.¹¹ Of interest, in contrast to established allergic diseases, EE has a striking gender predilection; 70–80% of the affected individuals are males.

Clinical presentation

The majority of adult patients with EE present with the characteristic oesophageal symptom of dysphagia for solid foods, often leading to long-lasting food impaction.^{5–7,11} A minority (between 20%¹⁵ and 42%¹⁶) experience retrosternal or upper abdominal pain not connected with the act of swallowing, but rather occurring spontaneously or induced by alcoholic or acidic beverages, e.g. white wine. This latter manifestation may mimic reflux disease, but typically persists despite therapy with proton pump inhibitors. The chronic inflammation does not interfere with the patient's physical well-being. In contrast to the non-affected health status, the quality of life is substantially diminished.² The physical examination is typically uneventful with the exception of the finding of co-existing allergic airway diseases, such as asthma or allergic rhinitis.

Endoscopic features

Unfortunately, the endoscopic signs of EE can be unremarkable, misleading,^{9,15,17} absent,⁵ or even dramatically change from one exam to the next. EE is therefore not defined by endoscopic criteria, but rather can only be unequivocally diagnosed based on oesophageal histology, as discussed below. To date, at least 12 different endoscopic signs have been reported, the leading ones being *reddish mucosal furrows*⁹ (Figures 1 and 2) and *loss of vascular pattern* (Figures 1, 3 and 4).¹⁷ Of note, both signs are subtle and may easily be missed during a routine endoscopy. In contrast, *white exudates* are more spectacular and easy to detect, but they are at risk for being misinterpreted as oesophageal candidiasis.¹⁸ This sign occurs in more than half of the EE patients and may take a variety of shapes and sizes, such as nodules, membranes (Figure 3), plaques and pinpoints (Figure 4).^{19,20} A histomorphometric analysis of these white exudates has demonstrated that they correspond to a dense accumulation of eosinophils.¹⁷ Because the eosinophilic infiltration may be inhomogeneous in EE, it is important to take biopsy samples from these white alterations in order to establish EE as a diagnosis. *Solitary rings* or *corrugated rings* (Figure 2) that impart a trachea-like aspect to the oesophagus and *strictures* of different sizes are further manifestations of EE. Finally, the finding of an abnormally fragile and inelastic mucosa, a so-called *crêpe paper oesophagus*, which tears even after minimal trauma, might be a pathognomonic sign of EE.¹⁹ Of note, all these signs rarely appear as a solitary alteration, but almost always in a random combination of up to five different abnormalities. EE therefore evokes a patchwork of different signs rather than a single, characteristic endoscopic picture. This heterogeneity, together with the usually discreet expression of the endoscopic

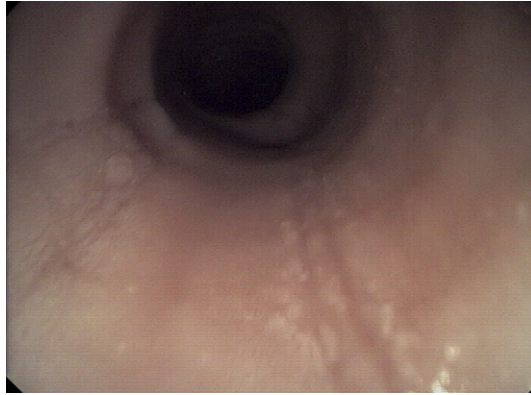


Figure 1. Endoscopic picture from a 34-year-old male patient with a 5-year history of dysphagia due to EE. The oesophagus displays longitudinal red furrows and loss of vascular pattern.

findings, hinders the endoscopic recognition of EE and may likewise contribute to its underdiagnosis.¹⁶

Histological features and immunopathogenesis

The established criterion for diagnosing EE is an *increased number of intraepithelial eosinophils* (Figure 5).²¹ Because endoscopic findings may be subtle and the eosinophilic infiltration is often inhomogeneous, biopsies should be taken from all patients in whom EE is among the differential diagnoses. Samples should be obtained regardless of the gross appearance of the mucosa, and multiple biopsies should be obtained from different oesophageal locations along the length of the oesophagus.⁸ The question of how many biopsy samples should be taken and which threshold value for eosinophils should be set as the diagnostic criterion is finally a question of the sensitivity of the 'endoscopy/histology' method. Gonsalves et al recently performed a retrospective analysis of



Figure 2. Endoscopic picture from a 42-year-old female patient, suffering from dysphagia for more than 20 years. Of note, the corrugated rings (trachea-like oesophagus) and red furrows.



Figure 3. Endoscopic picture from a 33-year-old male patient with a 5-year history of dysphagia due to EE, demonstrating an oesophageal mucosa with meadow-like, white exudates and loss of vascular pattern.

341 biopsies from 66 adults with EE to determine how the number of biopsy samples impacted diagnostic ability. The results showed that with a threshold of 15 eosinophils/HPF, the procurement of one biopsy had a sensitivity of 55%, in contrast to a sensitivity of 100% with five biopsies.¹⁶ Based on these data and on our personal experience, for clinical purposes, we recommend that in a patient with suspected EE, the endoscopy not be performed until a previous 4-week therapy with proton pump inhibitors has been undertaken. After this period, we further recommend that at least two biopsies from the proximal and two from the distal oesophagus be taken, and an infiltration of at least 15 eosinophils/HPF be used as the diagnostic threshold. Despite the fact that this is a feasible approach for diagnosing EE, it does not reflect the functional contribution of the eosinophils to the inflammatory process. Further markers, such as micro-abscess formation, signs of degranulation or signs of apoptosis, may better reflect the intensity of the ongoing eosinophilic inflammation than does the pure number of eosinophils. Other histological signs, including *superficial layering*, *basal zone hyperplasia*,



Figure 4. Endoscopic picture from a 51-year-old male patient, suffering from dysphagia due to EE for the past 20 years. One sees pinpoint-shaped white exudates and loss of vascular pattern.

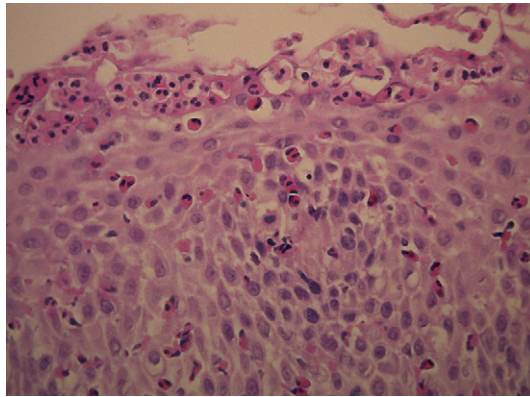


Figure 5. Photomicrograph of the oesophageal mucosa from a 44-year-old male patient with a 9-year history of dysphagia due to EE, showing a dense eosinophilic infiltration of the superficial layers of the squamous epithelium (HE staining; original magnification 400 \times).

papillary elongation, epithelial oedema and lamina propria fibrosis may support the diagnosis and help exclude other conditions with oesophageal eosinophilia.

As demonstrated with immunohistology, the inflammatory cell infiltration in EE consists not only of eosinophils; at least T cells and mast cells are also involved in the inflammatory response.²² In addition, an increased expression of IL-5, TNF-alpha and eotaxin-3 has been observed in the oesophageal epithelium of EE patients.^{22,23} Despite the fact that the interplay between these cellular and humoral components is not yet clearly understood, it has become clear that EE is a dominant T_H2-type inflammatory reaction.²⁴

Laboratory abnormalities

Unfortunately, despite our best efforts, non-invasive laboratory analyses have not yet been established for diagnosing EE or for the monitoring of this chronic disorder. Today, only the determination of peripheral blood eosinophils and total IgE levels have shown a certain clinical relevance, whereas all other non-invasive markers, e.g. eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) determination in the blood²⁵ require further validation.

Almost half of the patients with EE have a mild elevation of *eosinophils in the peripheral blood*.^{5,7} Furthermore, it has been demonstrated that, when compared with EE patients having normal eosinophil values, patients having peripheral eosinophilia have a less favourable course and suffer significantly more disturbance.² Determining the peripheral blood eosinophils can therefore be used to support the clinical and histologic diagnosis of EE, and serve as a predictor of the long-term course of the symptoms.

Between 60 and 70% of adult EE patients have elevated total *IgE levels*. However, it is not clear whether or not the total IgE can serve as a surrogate marker for disease progression or resolution. The only value of this marker is that patients with normal IgE levels respond better to treatment with corticosteroids than do patients with elevated levels.²⁶ This marker can therefore be used as a predictor of the therapeutic response to corticosteroid treatment.

Natural history and complications

Even the first comprehensive descriptions of EE in the early-1990s suggested that EE was a chronic disorder: patients often had a history of dysphagia for many years before the diagnosis was finally established.^{5,7} However, the final proof of EE's chronicity was furnished by a study that focused primarily on the disease's natural history and followed 30 patients for, on average, seven years.² The persistent dysphagia over years experienced by the vast majority of patients exerted a major negative impact on their quality of life. This analysis further showed that the eosinophilic infiltration persisted in all symptomatic patients. In adults, EE must therefore definitely be considered a chronic disorder with persistent or relapsing symptoms, and with a large probability of substantially diminishing the quality of life. Fortunately, it does not appear to limit the life expectancy, as so far no fatal outcomes have been reported in association with EE.

Nevertheless, if untreated, EE harbours all the risks of an uncontrolled and persistent inflammation. It is well established that a chronic and sustained eosinophilic inflammation can induce irreversible structure changes of the affected organ.²⁷ That this process happens in EE is supported by several studies which detected a relevant fibrosis in the subepithelial layers of the oesophagus.^{2,15,28,29} However, Aceves and colleagues recently provided evidence that structural alterations are present in the subepithelial layers of EE oesophagi and that these may be due to an increased TGF- β 1 expression.³⁰ These authors examined seven children with a healthy oesophagus, seven children with reflux oesophagitis and seven paediatric EE patients and found, in the subepithelial compartment of all EE patients, an oesophageal mucosa with significantly increased fibrosis, vascularity and vascular activation. Of interest, these alterations were not observed in their patients with reflux oesophagitis. This so-called remodelling of the oesophagus is likely the cause of several EE-inherent complications, such as stricture formation,³¹ pan-oesophageal narrowing, loss of elasticity of the mucosa,¹⁹ Boerhaave syndrome³² and secondary reflux disease due to a malfunction of the lower oesophageal sphincter.³³

Furthermore, the EE-associated oesophageal remodelling leads to an extremely fragile, inelastic and rigid oesophageal wall structure that increases the risk for complications with instrumental interventions. Because the oesophagus is a hidden organ, invasive procedures, such as upper endoscopies, removal of impacted food or dilation of strictures, are frequently required for diagnostic and therapeutic purposes in patients with EE. These interventions are generally accompanied by minimal pain and an almost negligible risk of injuries or perforation. In contrast, even after uneventful endoscopies, EE patients often suffer from odynophagia and, to date, four procedure-induced oesophageal perforations have been reported, most occurring after removal of impacted food by rigid endoscopy.³²

Treatment

No consensus has yet been reached regarding optimal treatment of EE. Specifically, the debate is still open as to whether the goal of therapy should be the *control of symptoms* or the *control of the inflammatory reaction*. As long as no controlled treatment studies are available which demonstrate that a consequent long-term anti-inflammatory therapy can prevent irreversible structural alterations and loss of oesophageal functions, the endpoint of the treatment is to control symptoms. However, it must be emphasised that control of symptoms means 'free of symptoms' and does not mean that the

patient learns how to ‘cope with symptoms’. Effective treatments for adult patients with EE include systemic^{34,35} or topical corticosteroids^{33,35–37} and oesophageal dilation.^{5,9,19,38} The value of biologicals, e.g., monoclonal antibodies against IL-5 or TNF-alpha in the treatment of corticosteroid-refractory or corticosteroid-dependent EE, still remains to be determined, despite some promising reports.^{39,40} In contrast to the treatment of children with EE, the value of dietary measures, such as elimination diets for adult patients, is still under discussion.^{41,42}

Based on our actual understanding of EE, we propose that a prudent course for managing symptomatic adult EE patients might be outlined as follows: If endoscopy detects no severe stenosis, the first line therapy should be medical treatment with topical corticosteroids. Fluticasone or Budesonide, 1 mg twice a day, sprayed into the back of the throat and swallowed rather than inhaled, for 2–4 weeks. This therapeutic course has been shown to induce clinical and histologic remission in at least 70% of EE cases. Patients must be instructed not to eat or drink for 30 minutes following the actuation. This approach has almost no systemic side effects, but oro-pharyngeal and oesophageal candidiasis have been reported. Whether this induction treatment should be followed by a low dosage maintenance therapy is not yet clear and mainly depends on the duration of the achieved remission. Patients in whom stenoses prevent endoscope passage should be treated with dilation.¹⁹ *Nota bene*: this intervention must be performed less aggressively in EE patients than in patients with non-EE oesophageal stenoses.³² In patients refractory to Fluticasone or Budesonide, systemic corticosteroids should be considered. Finally, in patients with symptoms dependent on, or refractory to, systemic corticosteroids, immunosuppressants⁴³ or IL-5 blocking agents should be evaluated (see Figure 6).^{39,40} After therapy has been established, we recommend that patients be followed-up, both clinically and endoscopically, in order to ensure that symptoms have resolved and mucosal healing has occurred. Finally, we must underscore that the number of properly performed therapeutic trials is still limited. These recommendations reflect our current standard of knowledge: they may change in the near future.

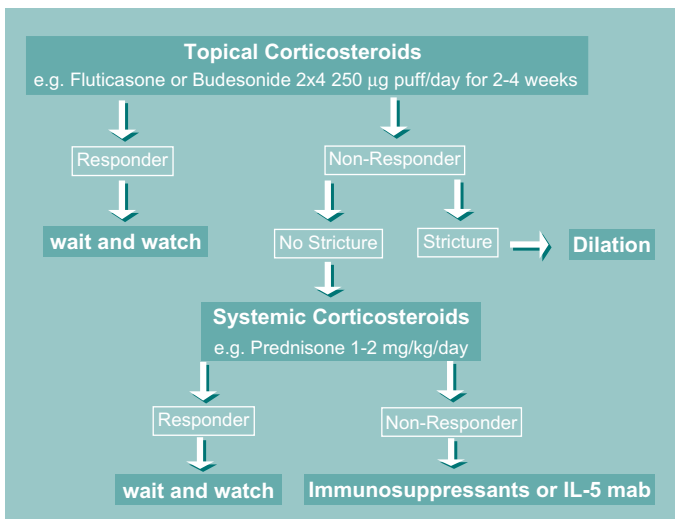


Figure 6. Therapeutic management of EE in adults.

IDIOPATHIC EOSINOPHILIC GASTROENTERITIS

Definition and classification

Eosinophilic gastroenteritis (EGE) comprises a poorly defined pool of uncommon and likely heterogeneous diseases. They all are characterised by a prominent and recurrent⁴⁴ eosinophilic tissue infiltration of the gastrointestinal tract of unknown origin.⁴⁵ The diagnosis is based on the following three criteria: (1) non-specific gastrointestinal symptoms; (2) eosinophilic infiltration of one or more areas of the gastrointestinal tract; and (3) exclusion of other causes for the intestinal eosinophilia.⁴⁶ No consensus has yet been reached regarding the histological criteria for diagnosing EGE. This may be due to the fact that the healthy gastric and intestinal mucosa harbour eosinophils under physiological conditions, but normal cell numbers have not yet been established.

EGE may be sub-classified either according to the segments of the gastrointestinal tract affected by the process, or according to the depth of the eosinophilic infiltration. With respect to the segmental classification, it is important to recall that the entire gastrointestinal tract may be involved in EGE,⁴⁷ or it may be restricted to isolated organs, such as the oesophagus,^{48,49} the stomach,^{50–52} the small bowel and the colon,⁵³ liver, biliary tract,⁵⁴ pancreas⁵⁵ and peritoneum.⁵⁶ The latter, Klein's classification system, distinguishes between mucosal, muscular and serosal forms of EGE.^{45,47,57} Parasitic infections, inflammatory bowel disease, connective tissue diseases, side effects of drugs⁵⁸ and lymphoproliferative malignancies⁵⁹ must be ruled out before a diagnosis of EGE can be established.

Epidemiology and natural history

Except for the serosal form where 75% of patients are women 40 years or older,⁶⁰ EGE is predominantly a male disorder⁶¹ that affects children as well as adults.^{45,47} Unlike EE, EGE seems to be rather a rare disease. During the 70 years since it was first described by Kaijser in 1937,⁶² the literature reports slightly more than 200 cases. However, one recently presented study performed in a single, population-based gastroenterology practice identified a further 30 EGE patients within an 8-year period (0.67% frequency of diagnosis with upper endoscopies),⁶¹ suggesting that EGE might be more common than previously assumed. Despite the fact that EGE is likely a chronic disorder, its natural course is still not defined.

Clinical presentation

The clinical manifestations of EGE depend on its location within the gastrointestinal tract and on its depth of infiltration. Mucosal involvement, the most frequent subtype, is typically associated with vomiting, diarrhoea, abdominal pain, weight loss and failure to thrive due to malabsorption and protein-losing enteropathy.^{47,50,63,64} Occult or frank bleeding, with or without iron deficiency anaemia and obstructive jaundice,⁶⁵ are further manifestations of mucosal disease. Affliction of the muscular layers may lead to signs and symptoms of intestinal obstruction⁶⁶ and acute abdomen,⁶⁷ whereas patients with serosal involvement typically complain of bloating and have ascites.⁵⁶ Transmural involvement of the stomach may even lead to acute gastric perforation.⁶⁸ Peripheral blood eosinophilia is seen in approximately two-thirds of EGE patients.⁴⁷

Diagnostic measures

The mucosal form of the disease has the advantage that the alterations can be seen on endoscopy. Today all segments of the gastrointestinal tract can be visualised using upper endoscopy, ileocolonoscopy, double-balloon enteroscopy or capsule endoscopy. Typical findings include thickening of the intestinal folds with deformation of the luminal configuration, diminished peristalsis, as well as an erythematous and friable mucosa with lesions. Additionally, conventional endoscopy enables representative biopsy samples to be taken for histologic confirmation of the diagnosis,^{51,53,69,64} where eosinophils are noted in the involved layer.⁷⁰ Patients with suspected serosal disease should be evaluated by laparoscopy, where the findings for this form of EGE include ascites, whitish nodules and thickening of both the parietal and visceral peritoneum.⁵⁶ To distinguish between serosal EGE and other peritoneal infiltrations, e.g., carcinosis or tuberculosis, histologic and cytologic examinations of biopsy specimens and ascites are mandatory.

The muscular form of the disease can be detected by CT scan or conventional radiological examinations, but these methods are hampered by the difficulty encountered in taking histologic samples for diagnosis confirmation. Most reported cases of muscular disease were diagnosed during surgical resection of an intestinal obstruction or suspected malignancy.

Treatment

EGE is an uncommon disease and, as such, no prospectively performed therapeutic studies are available. In the literature, case reports and small case series have reported a positive impact from a variety of agents, including corticosteroids,^{50,52,61} proton pump inhibitors,⁶¹ mast cell stabilisers,^{71,72} antihistamines,⁷³ leukotriene antagonists,⁷⁴ restriction diets,^{50,52} the somatostatin analogue, octreotide,⁶⁴ as well as surgical resection of stenosed intestinal segments.^{55,66}

While patients with the serosal type respond dramatically to steroid therapy (Durie's study cites a 90% response⁶⁰), optimal treatment is yet to be found for other EGE forms. Based on these data, we propose first attempting proton pump inhibitors. If the course of the disease proves refractory, systemic corticosteroids should be considered. Unfortunately, the relapsing nature of the ailment harbours the risk of corticosteroid side effects, and leukotriene inhibitors should be evaluated in patients with frequent flare-ups. For patients with allergy-associated EGE, a restriction diet could be a valuable alternative.

HYPEREOSINOPHILIC SYNDROMES WITH GASTROINTESTINAL INVOLVEMENT

Definition and classification

The hypereosinophilic syndromes (HESs) are a heterogeneous group of rare disorders, characterised in the past by: (1) persistent peripheral blood eosinophilia with more than 1500 cells/mm³ for longer than 6 months; (2) no known cause of eosinophilia; and (3) signs and symptoms of organ involvement.^{3,75,76} Recent efforts have begun reclassifying this heterogeneous group of disorders according to the recognition of several clinical subtypes and new biomarkers.⁴ Currently recognised subtypes include

PDGFRA-associated HES, lymphocytic variant HES, chronic eosinophilic leukaemia and familial eosinophilia.⁴ Independent of this subclassification, the eosinophilic infiltration may affect the cardiovascular system (90%), the peripheral and central nervous systems (90%), including the retina, the coagulation system (80%), the skin (55%), the respiratory system (50%), the liver and spleen (35%), as well as the gastrointestinal tract (25%).

Epidemiology and natural history

HES is similar to the other idiopathic eosinophilic disorders in that it is also a predominantly male condition where the male-to-female ratio averages 3:1. The onset of the disease commonly occurs between the ages of 20 and 50 years.^{77,78} Data reporting its prevalence or incidence are not available.

Clinical presentation

HES typically has a gradual onset. At the beginning, patients complain of general symptoms, such as anorexia, fatigue, weight loss, fever, abdominal pain and night sweats. Throughout the course of the disease, the clinical manifestations depend on the end organs involved. With gastrointestinal involvement, the leading sign is hepatosplenomegaly, evoked by eosinophilic infiltration or congestive heart failure. Abdominal pain and diarrhoea with malabsorption have also been reported. When only the digestive tract is involved, it may prove difficult to distinguish between HES and EGE. During its long-term course, extraintestinal manifestations or lymphoproliferative conditions may appear and facilitate the definite diagnosis.⁷⁹ The ultimate prognosis depends on whether there is end organ damage. Patients with intestinal manifestations and cardiac involvement have a rather poor prognosis with the risk of fatal outcome, whereas those with skin disease generally endure a milder course.⁷⁶

The presentation of the mucosal alterations in HES with intestinal involvement is similar to that observed in patients with EGE (see above). Even though endoscopy does not permit a definite identification, it does permit histological characterisation of the lesions and is thus an important procedure in the diagnostic work-up of patients with peripheral eosinophilia and abdominal symptoms. In patients with hepatic or splenic enlargement, a CT scan or ultrasound examination with liver biopsy may be an appropriate diagnostic approach.

Immunopathogenesis

It is likely that HES encompasses several disease processes with different pathogenic mechanisms. Several authors have demonstrated a significant elevation of the eosinophilopoietic cytokine IL-5 in the serum of patients with HES.^{79–81} The mechanisms of IL-5 overproduction can involve a T_{H2} lymphocyte response in allergic and parasitic diseases, an expansion of IL-5 producing T cells in patients with neoplastic or pre-neoplastic lymphoproliferative disorders,⁷⁹ or an activation of gene transcription due to a chromosomal translocation.⁸² Recently, an IL-5-independent form of HES has been described in which a tyrosine kinase is overexpressed as a consequence of gene fusion.⁸³ This broad spectrum reflects the heterogeneity of underlying mechanisms that leads to the common clinical manifestation of HES. Despite their apparent diverse aetiologies, they share the common feature of eosinophil-mediated end organ tissue damage.⁸⁴

Treatment

Comparable to EGE, HES is a rare disorder and no prospective treatment studies have been carried out to date. Treatment strategies for patients with HES are based on regimens aimed at lowering the eosinophil level. Corticosteroids have been used for decades in the treatment of HES and, with the exception of PDGFRA-associated HES, remain the first-line therapy.⁸⁵ Cytotoxic agents, such as hydroxyurea, vincristine and chlorambucil, have been successfully used with corticosteroid-refractory patients.³ Interferon- α is reported to be a useful agent in patients with mucosal ulcerations.⁸⁶ Cyclosporine, another immuno-modulatory agent directed against expanded T cells, is often used in combination with low doses of corticosteroids. Patients with HES often have high levels of IL-5, and monoclonal antibodies against this peptide mediator could prove to be a valuable approach.⁸⁷

Recently, imatinib mesylate, a tyrosine kinase inhibitor, has shown to be a highly active drug in inducing prolonged remissions in patients with PDGFRA-associated HES.^{4,83}

SUMMARY

This review underscores that much ground still remains to be covered in diagnosing and treating patients with the three common EGID.

EE, the most frequently seen EGID, is chronic and difficult to diagnose with its confusing endoscopic features. Patients, usually males, typically present with recurrent dysphagia and food impaction as well as co-existing allergic airway diseases. Untreated EE induces irreversible structural changes of the oesophagus: remodelling leads to an extremely fragile and rigid oesophageal wall structure that increases the risk for complications, including perforation. Effective treatments for adult patients with EE include systemic or topical corticosteroids and oesophageal dilation. Though the quality of life is substantially diminished in this chronic disorder, life expectancy is not affected.

EGE, a rather rare and predominantly male disorder, may involve the entire gastrointestinal tract or be restricted to isolated organs in mucosal, muscular and serosal forms. Clinical manifestations depend on location and infiltration depth. Mucosal involvement, the most frequent subtype, is typically associated with vomiting, diarrhoea, abdominal pain and weight loss. The muscular form may mimic intestinal obstruction or acute abdomen. Patients with the serosal form (75% are women over 40) complain of bloating and ascites, and usually respond dramatically to corticosteroids.

The HES are a heterogeneous group of rare disorders, characterised by persistent peripheral blood eosinophilia with more than 1500 cells/mm³ for longer than 6 months, no known cause of eosinophilia, and signs and symptoms of organ involvement. Prognosis depends on the degree and location of the eosinophil-mediated end organ tissue damage.

Practice points

- Eosinophilic gastrointestinal diseases are an enigmatic and relatively common group of diseases with a wide variety of presentations, with eosinophilic oesophagitis the most well described.

- Adult patients with eosinophilic oesophagitis present with oesophageal-related symptoms, such as dysphagia, food impaction and non-swallowing related retrosternal pain.
- A high index of suspicion is needed to look for these diagnoses, as their presentation overlaps with the more common GERD.
- Treatment with corticosteroids is effective, but relapses are frequent once treatment is discontinued.

Research agenda

- Natural history studies;
- Non-invasive measurements of eosinophilic inflammation;
- Controlled treatment trials of newer therapies, as well as non-pharmacologic means of managing disease;
- Studies of pathogenesis.

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