Review paper

Eosinophilic gastroenteritis – a manifestation of an allergic disease in the gastrointestinal tract? Part 1. Epidemiology and diagnosis

Andrzej Kuźmiński[1], Tomasz Rosada[1], Justyna Przybyszewska[2], Natalia Ukleja-Sokołowska[1], Zbigniew Bartuzi[1]

[1]Department of Allergology, Clinical Immunology and Internal Diseases, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

[2]Department of Nutrition and Dietetics, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

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Address for correspondence: Andrzej Kuźmiński MD, PhD, Department of Allergology, Clinical Immunology and Internal Diseases, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, phone: +48 501 006 104, e-mail: jendrek75@interia.pl

Abstract

Eosinophilic gastroenteritis (EGE) is a relatively rare disease, but it should be considered whenever a patient presents with unexplained gastrointestinal symptoms that cannot be explained by parasitic infection or other gastrointestinal diseases characterized by eosinophilic infiltration. A high coexistence of EGE and allergic diseases has been documented. Diagnosis of EGE is based primarily on clinical, endoscopic, and histopathological findings. Glucocorticosteroids and other immunomodulatory drugs are the mainstay of treatment, but currently the greatest hope lies in biological drugs, which are undergoing intensive research. This disease is troublesome for the patient and significantly reduces the quality of life.

Introduction

In recent years there have been many studies emphasizing the role of eosinophilic oesophagitis as an important component in the diagnostic process in patients with dyspepsia symptoms, especially with coexisting symptoms of allergic diseases or predisposition to them in the form of atopy. Much less attention is focused on the inflammatory process involving eosinophilia in the later parts of the gastrointestinal tract [1].

Eosinophilic gastroenteritis (EGE) is a rare disease characterized by inflammatory infiltrates of the gastrointestinal wall mainly composed of acidophilic cells. The exact pathomechanism of the disease has not been clearly defined. Despite the fundamental character of eosinophils in the development of the disease, it seems that dysregulation of the balance between Th1, Th2, Th3, and Th13 lymphocytes may play the main role. In this disease there is a promotion of Th2 lymphocytes connected with the production of such cytokines as interleukin 4 (IL-4), IL-5, or IL-13 and chemokines (eotaxin-1 and -2), which results in recruitment, activation, and stimulation of eosinophil survival and antigen-specific production of sIgE [2, 3]. This results in the prolongation of eosinophil survival and the formation of eosinophilic infiltrates in the gastrointestinal wall, which in turn leads to the development of EGE.

Epidemiology

EGE is a rare disease. Since 1970, about 300 cases have been reported, about 44–63% of whom had EGE coexisting with allergic disease (mainly asthma, allergic rhinitis, allergic urticaria, and contact eczema). It is also believed that the disease can often be associated with food allergy (mainly milk, egg, peanut) and the use of certain medications (enalapril, rifampicin, naproxen, bromazepam). The prevalence of the disease is estimated at 1–20 cases per 100,000. Most cases are Caucasian, and the disease is slightly more commonly diagnosed in men (1.1 : 1). Due to the increasing prevalence of allergic diseases and a gradual increase in physicians' awareness, EGE is diagnosed more and more frequently, which at the same time affects the interest in the subject and stimulates research on its pathogenesis and the best possible treatment [1, 4].

Symptomatology

The first symptoms of eosinophilic gastroenteritis most often appear in adolescents and young adults, but they may occur in any age group. In the literature the first symptoms of the disease were described in a 25-day-old infant as well as in a 77-year-old man [5]. The symptomatology is not very characteristic and lacks pathognomonic symptoms. The most common symptoms of the disease are summarized in Table I. The location of the inflammatory process sometimes translates into the character of complaints: when lesions are located mainly in the stomach, pain is the dominant symptom, whereas when lesions are located in the small or large intestine, abdominal pain, diarrhoea, and the presence of blood in the stool predominate. Additionally, the symptoms also change depending on the depth of the inflammatory infiltration of the gastrointestinal wall and may be partially masked by symptoms of allergic co-morbidities [6]. The coexistence of food allergy, whose symptoms and pathomechanism largely overlap with eosinophilic gastroenteritis, may pose additional diagnostic difficulties [7, 8].

Diagnostics

The main criteria for diagnosing the condition include the following:

1. Presence of gastrointestinal symptoms.
2. Histological demonstration of eosinophil infiltration in the gastrointestinal tract or the presence of large numbers of eosinophils in ascetic fluid.
3. Exclusion of other causes of tissue eosinophilia.

Table I. The most common symptoms of eosinophilic gastroenteritis, including the main pathological types

Mucosal type (57–100% of cases)
• Abdominal pain • Nausea • Vomiting • Diarrhoea • Impaired absorption • Hypoalbuminaemia • Anaemia • Weight loss • Gastrointestinal bleeding
Muscular type (30–70%)
• Spasmodic abdominal pain • Nausea • Vomiting • Gas and stool retention • Abdominal bloating
Serous type (4.5–9%)
• Eosinophilic ascites • Peripheral eosinophilia • Peritonitis • Intestinal intussusception

Unfortunately, there is no clear algorithm and "GOLDEN STANDARD" for diagnosis and treatment. The diagnosis is usually established based on a detailed history, including allergic history, as well as laboratory tests, endoscopy, imaging, and histopathological examination of tissues involved in the inflammatory process.

Laboratory tests

Approximately 80% of EGE cases have peripheral blood eosinophilia, based on which the disease is classified as mild (600–1500 eosinophils/µl), moderate (1500–5000 eosinophils/µl), and severe (> 5000 eosinophils/µl). The mean blood eosinophil levels in patients with EGE are higher than in patients with eosinophilic esophagitis (2130/µl vs. 446/µl), which seems to be a good indication with which to differentiate between these 2 disease entities. It has been documented that the highest eosinophil levels occur when the lesions are located in the small intestine (mean 2656 eosinophils/µl). Other laboratory abnormalities include iron deficiency anaemia, hypoalbuminaemia, and elevated IgE levels (≥ 100 IU/ml) in 2/3 of patients [9]. The disease also frequently leads to disorders of protein and fat digestion and absorption. Protein digestion disorders are assessed by measuring α1-antitrypsin levels in a 24-hour stool collection. Normal α1-antitrypsin levels range from 0 to 54 mg/dl and are strongly elevated in patients with EGE. Protein loss may also result in low immunoglobulin levels, but this does not preclude concomitant elevation of serum IgE levels. Fat digestion disorders are usually manifested by fatty diarrhoea, which occurs in about 30% of patients, whereas when there is serum involvement there is a presence of exudative fluid in the peritoneal cavity with a predominance of eosinophils, reaching about 90% of all white blood cells found [10, 11].

Endoscopic examinations

Gastrointestinal endoscopic diagnosis remains the method of choice for the diagnosis of eosinophilic gastroenteritis. During the examination a picture varying from normal mucosal appearance, through erythematous, nodular changes, ulceration and mucosal fragility, or the presence of pseudopolyps, to diffuse inflammatory changes with the total loss of villi, infiltration of the gastrointestinal wall, with the presence of submucosal oedema and gastrointestinal wall fibrosis leading to the loss of their elasticity can be visualized. Endoscopic biopsy plays an important role in the diagnosis, but it is of limited value due to the patchy distribution of eosinophilic infiltrates, requiring at least 6 samples from both normal and abnormal mucosa to avoid the possibility of diagnostic error. Endoscopic ultrasound examination seems to be useful, especially for the evaluation of

Table II. Normal number of eosinophils on histopathological examination according to location in the gastrointestinal tract

Location	Adults	Children
Duodenum	< 19 eosinophils/HPF	< 10 eosinophils/HPF
Caecum	Up to 50 eosinophils/HPF	Up to 40 eosinophils/HPF

muscularis and serosal types, because it allows biopsies to be taken from the lesion sites using fine-needle aspiration biopsy [12–14].

Radiological diagnostics

Radiological changes are nonspecific and present in only about 40% of patients with EGE. Standard review abdominal radiographs sometimes show thickening of the gastric folds with filling defects and signs of pyloric stenosis, especially in the muscularis type with local involvement of the antrum and pylorus. The small and large intestines may be dilated or narrowed with increased wall thickness and mucosal folds. Ultrasound examination also lacks pathognomonic features and most often shows ascites, bowel wall thickening, and local lymphadenopathy. In abdominal X-ray ascites, gastrointestinal wall oedema, intestinal stenosis, and "halo" sign were most frequently described. Radioisotopic examination with the use of leukocytes labelled with technetium (99mTc) is very interesting and useful in the assessment of the extent and monitoring of therapeutic response, but it is of little diagnostic value. This method allows for the assessment of the disease process advancement in a given tissue, based on the increased recruitment of lymphocytes to the sites of active inflammation. However, it does not enable differentiation of the cause of inflammation; moreover, its availability is significantly limited, which makes it of no value in the diagnostic process of EGE [15–19].

Histopathological diagnosis

Gastric and duodenal biopsy specimens taken during endoscopic examinations are the basis for the diagnosis of eosinophilic gastroenteritis. Much more accurate methods include laparotomy or at least exploratory laparoscopy, which provide full-thickness specimens and thus facilitate the diagnosis of myometrium and serous membranes; however, due to their invasiveness they can be categorized as casuistic. When taking specimens, it is important to take them from both normal- and abnormal-looking mucosa and to accurately determine the location, because the normal eosinophil count varies depending on the anatomical location of the gastrointestinal tract (Table II) [20–22].

Once eosinophilic infiltration is confirmed, diseases associated with eosinophilia should be excluded, such as the presence of intestinal parasites, eosinophilic esophagitis (EoE), celiac disease, protein-losing enteropathy, cow's milk protein intolerance, or idiopathic hypereosinophilic syndrome.

The disease entities that should be excluded during the differential diagnosis of EGE are summarized in Table III.

Table III. Differential diagnosis of EGE

Disease entity	Features helpful for diagnosis
Parasitic intestinal infestation	Faecal examination for the presence of adult forms of parasites, their fragments, or eggs can provide many diagnostic clues, which are the basis for confirmation of infection with a specific parasite and implementation of effective treatment
Eosinophilic oesophagitis	In EoE, eosinophilia is restricted to the oesophagus only. Typically, eosinophils are found near the epithelial surface, and characteristic striations or furrows can be seen on the oesophageal mucosa during endoscopy
Celiac disease	The diagnosis should include immunologic studies and characteristic features on endoscopic and histopathologic examination, i.e. villous atrophy and hypertrophy of crypts in the small intestine and predominant lymphocyte infiltration in the crypts
Hypereosinophilic syndrome	Hypereosinophilic syndrome is a myeloproliferative disorder characterized by peripheral eosinophilia exceeding 1500 eosinophils/HPF persisting for more than 6 months. In addition to the gastrointestinal tract, the heart, CNS, lungs, liver, skin, and kidneys are also involved, with > 55% of patients having severe complications in one or more of these sites. The syndrome can be ruled out when there is no eosinophilic infiltrate in all other organs except the intestine
Autoimmune vasculitis	The basis of diagnosis is immunological examination and histopathological picture

Summary

Eosinophilic gastroenteritis is not a common disease, but it should be considered during the diagnosis of gastrointestinal disorders. Available scientific studies have not observed differences in survival between individuals with EGE and healthy subjects, but an impact on the development of children and adolescents has been documented, which has been reflected in the ultimate growth of the patient. If the disease develops in infancy and specific food allergens can be identified that are pathogenetically linked to clinical symptoms, the probability of achieving remission of the disease is high. Moreover, a high absolute eosinophilia count at diagnosis was found to be an independent predictor of relapse, as was extensive intestinal involvement. Observations and studies have shown that EGE has a good prognosis and is not associated with malignancies.

Eosinophilic gastroenteritis should be considered whenever a patient has unexplained gastrointestinal symptoms that cannot be explained by parasitic infection or other gastrointestinal diseases characterized by eosinophilic infiltration.

Conflict of interest

The authors declare no conflict of interest.

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