REVIEW
DERLEME

# Eosinophilic gastroenteritis
# Eozinofilik gastroenterit

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## SUMMARY

Eosinophilic gastroenteritis is a T helper 2 mediated allergic disease characterized by intense eosinophilia in the stomach and small intestine. Although it was first described in 1937, its pathogenesis is still not clearly established. Eosinophilic gastroenteritis is included in the group of eosinophilic gastrointestinal disorders and is divided into three subtypes: eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis. The most prominent feature of eosinophilic gastroenteritis is tissue eosinophilia. Clinical manifestations of eosinophilic gastroenteritis may differ depending on the site of involvement in the gastrointestinal system and the depth of invasion in the intestinal wall. However, the most common clinical symptoms are abdominal pain, nausea, vomiting, diarrhea, weight loss, and gastrointestinal bleeding. Since eosinophilic gastroenteritis is a rare disease, there are no specific diagnostic criteria for diagnosis. However, the presence of four main criteria is important for diagnosis. These criteria are; presence of gastroinsetinal symptoms, eosinophilic infiltration of the gastrointestinal tract, exclusion of other causes of intestinal eosinophilia (parasitic infections, side effects of drugs, inflammatory bowel disease (IBD), connective tissue diseases and lymphoproliferative malignancies) and absence of involvement in other systems. Clinical history, physical examination, laboratory results, endoscopic and radiological findings are used for definitive diagnosis. Agents such as diet therapy, glucocorticoids, immunosuppressive agents, mast cell stabilizers, leukotriene antagonists, anti-IL5 antibodies and anti-IgE antibodies are used in the treatment of eosinophilic gastroenteritis.

**Keywords:** Abdominal pain, corticosteroids, eosinophili, eosinophilic gastroenteritis

## ÖZET

Eozinofilik gastroenteritis, mide ve ince bağırsakta yoğun eozinofili ile karakterize, Th2 aracılı alerjik bir hastalıktır. İlk olarak 1937 yılında tanımlanmasına rağmen patogenezi hala net olarak ortaya konamamıştır. Eozinofilik gastroenteritis, eozinofilik gastrointestinal bozuklar grubu içinde yer alır ve eozinofilik gastrit, eozinofilik enterit, eozinofilik kolit olmak üzere üç alt tipe ayrılır. Eozinofilik gastroenteritin en belirgin özelliği dokuda eozinofili tablosudur. Eozinofilik gastroenteriin klinik bulguları, gastrointestinal sistemdeki tutulum yerine ve bağırsak duvarında invazyon derinliğine göre farklılık gösterebilmektedir. Bununla birlikte en sık izlenen klinik belirtiler abdominal ağrı, bulantı, kusma, diare, kilo kaybı, gastrointestinal kanamadır. Eozinofilik gastroenteritis nadir izlenen bir hastalık olduğundan tanıda spesifik tanı kriterleri bulunmamaktadır. Ancak tanı sırasında dört ana kriterin varlığı önemlidir. Bu kriterler; gastroinsetinal semptomların bulunması, gastrointestinal sistemin eozinofilik infiltrasyonu, bağırsak eozinofilisinin diğer nedenlerinin (paraziter enfeksiyonlar, ilaçların yan etkileri, inflamatuar bağırsak hastalığı (IBH), bağ dokusu hastalıkları ve lenfoproliferatif maligniteler) dışlanması ve diğer sistemlerde tutulumun gözlenmemesi şeklindedir. Kesin tanı için klinik öykü, fizik muayene, laboratuar sonuçları, endoskopik ve radyolojik bulgular kullanılır. Eozinofilik gastroenterit tedavisinde diyet tedavisi, glukokortikoidler, immünsupresif ajanlar, mast hücresi stabilizatörleri, lökotrien antagonistleri, anti-IL5 antikoru, Anti-IgE antikoru gibi ajanlar kullanılmaktadır.

**Anahtar kelimeler:** Abdominal ağrı, eozinofili, eozinofilik gastroenterit, kortikosteroidler

## INTRODUCTION

Physiologically, eosinophils are observed in other parts of the gastrointestinal system other than the esophagus (1). The role of eosinophils is to defend against infectious agents and they are part of the innate immune system (2). In the gastrointestinal system, eosinophils physiologically exist between the 2 lamina propria of the small intestine and provide protection (3).

The main focus of the article is EG, a Th2 allergic disease within the group of primary eosinophilic gastrointestinal disorders, often characterized by intense eosinophil infiltration in one or more layers of the stomach and small intestine, causing organ dysfunction and clinical symptoms (4). EG; It is divided into three subtypes: eosinophilic gastritis, eosinophilic enteritis, and eosinophilic colitis. There is also a pathological classification divided into 3 according to the layer depth in the tissue (5).

Peripheral eosinophilia is frequently observed in EG. Therefore, diseases associated with peripheral eosinophilia such as eosinophilic granulomatous polyangiitis (EGPA) and hypereosinophilic syndrome should be ruled out before making a diagnosis (4). However, it should also be distinguished from diseases of the gastrointestinal system that show eosinophilic infiltration. It is known to be associated with atopy and allergy in the absence of the above-mentioned reasons (6).

Case series of EG are limited to either a single case or a small number of case groups (7). Because it is a disease that is difficult to diagnose, it is among the rare diseases (8). Although difficult to diagnose, it responds highly to diet and corticosteroid treatments in the correct diagnosis (7).

## EPIDEMIOLOGY

EG is a rare disease. However, with the increasing prevalence of allergic diseases such as bronchial asthma and allergic rhinitis, the number of cases of EG is increasing (9). However, the exact prevalence of EG is unknown (10). It has been reported that the number of patients diagnosed with EG has recently increased in the USA (11). The prevalence of EG is estimated to be 22-28 per 100,000 people in the USA (12). The prevalence of EG in western countries is 5-8/100,000 (13).

EG can occur in all age groups and in all races. However, the average age of incidence of EG is between 30 and 50 years (4,10). On the other hand, no data were available on the age-related change in the prevalence of EG (4). However, there are data that the prevalence of cases with bowel involvement tends to increase in childhood (14). There is no clear difference between genders in terms of the incidence of EG (4). In a study conducted in the USA, the prevalence of EG was shown as 8.4/100.000. In this ratio, women are more dominant (14). However, some different studies have shown that the number of men is slightly higher (15). There are few epidemiological data on the prevalence and incidence of EG in Asian countries (4). But among asians and whites (caucasians); Differences in gastrointestinal symptoms are likely due to differences in dietary habits and the prevalence of infectious agents (such as H.pylori) (16). Approximately 70% of patients with EG have a history of allergic disorders such as asthma, hay fever, hypersensitivity to drugs or eczema (15). The period from the onset of symptoms to the diagnosis is approximately 6-12 months. Symptoms may increase or decrease over the course of the disease. Because EG is a rare disease, epidemiological data are limited (17).

## PATHOPHYSIOLOGY

Although EG was first described in 1937 and studies have shown that it is associated with hypersensitivity reactions, its pathogenesis is still unclear (17,18). EG is thought to be caused by a chronic Th-2-type eosinophil allergic reaction, mainly due to food allergens (15,17). Many diseases are thought to cause a similar histopathological picture (19). The most prominent feature of EG is tissue eosinophilia (4,19). Normally, eosinophils are regulated by chemoattractants and are found in the lamina propria of the gastrointestinal tract (15,20). Eosinophils are involved in mucosal immunity in the gastrointestinal system (20). In many disease states such as parasitic infections and allergic diseases, an increase in the number of eosinophils is observed (1,15). The most important chemoattractants that recruit eosinophils are eotaxins (18,21). Interleukin-3 (IL-3) from T-helper 2 cytokines and CCL-26 / Eotaxin-3 from its chemokines in eosinophil up-regulation; Eotaxin-1, Interleukin-5 (IL-5) and Interleukin-15 (IL-15) have been shown to be effective in numerous studies (17). It has been shown that interleukin-5 increases eosinophil migration from bone marrow to tissues (18). In clinical studies in patients with EG, the amount of eosinophils in the blood was found to correlate with plasma IL-5 and IL-15 concentrations (22). In addition, eotaxin-1 and α4β7 integrin regulates the placement of eosinophils in the lamina proria in the stomach and small intestine (21). Eosinophils include a variety of factors involved in the inflammatory process in the stomach and intestinal wall seen in EG (23). These factors are major basic protein (MBP), eosinophilic neurotoxin (EDN), eosinophilic cationic protein (ECP) and eosinophilic peroxidase (EPO) (1,15). These substances are cytotoxic to the gastrointestinal epithelial structure (15,17,18). After the eosinophils are activated, tissue damage begins to develop with the release of these factors, thus triggering degranulation of mast cells and release of cytokines (15). Cytokines produced by Th-2 cells such as IL-4 and IL-13 may also be effective in eosinophilic inflammation (24). Further studies should be conducted to fully reveal the functions of increased serum thymic stromal lymphopoietin (TSLP), IL-33 levels and overactivation of TH-17 among other possible factors

that are thought to have an effect on the pathophysiology of the disease (17).

**CLINICAL PRESENTATION**

The clinical manifestations of EG may differ depending on the site of involvement in the gastrointestinal tract and the depth of invasion in the intestinal wall (25).

In the study conducted on 44 patients, the most common symptoms were vomiting (71%) and abdominal pain (62%) (25). In the study conducted on 22 Korean infant and pediatric patients, the patients were divided into two as histological EG (HEG) and probable EG (pEG) in patients in the hEG group; Hematemesis is the most common symptom in infants with 53.8% and abdominal pain in children with 60%. According to the patient's history, suspected allergens were determined as cow's milk (76.9%), egg whites (15.4%), crab (7.7%) and peach (7.7%). In the pEGE group, the first symptoms were 44.4% melena, 33.3% recurrent abdominal pain, 22.2% hematemesis and 11.1% vomiting. Suspected allergens were identified as cow's milk (55.6%), egg whites (11.1%), tree nuts (11.1%) and shrimp (11.1%) according to the patient's history (26).

Most of the clinical signs of EG are non-specific. These symptoms are abdominal pain, nausea, vomiting, diarrhea, weight loss, gastrointestinal bleeding, intestinal malabsorption and ascites (25). In addition to these clinical signs, growth retardation, growth retardation, delayed puberty, or amenorrhea may be observed in children and adolescents (10). In addition, many cases have atopy and allergy (25). Rarely, eosinophilic gastritis has been associated with autoimmune connective tissue diseases (27).

Eosinophilic infiltration can also lead to pancreatitis by causing edema, fibrosis, and distortion in the ampulla and periampullary duodenum (28).

EG is divided into three groups based on the clinical signs and depth of eosinophilic infiltration (5). These; mucosal form, muscular form and serosal form.

Mucosal form is the most common form among the three groups (25–100%) (15). It is most common because of its high availability with routine endoscopy and biopsies (15). In the mucosal form, it is presented with more vomiting, dyspepsia, abdominal pain, diarrhea and blood in the stool, iron deficiency anemia, malabsorption, protein-losing enteropathy and developmental disorders in children (29). Common findings in patients with mucosal EG are atopy and elevated serum IgE levels (15).

The muscular form is the second most common form (15). It is diagnosed in 13-70% of all cases of EG (15). In the muscular form, eosinophil infiltration is generally observed in the muscularis layer. Generally, the clinical signs are abdominal pain, vomiting, dispeptic symptoms, bowel obstructions, pyloricstenosis, and gastrointestinal obstruction symptoms mimicking gastric outlet syndrome (29). Stomach and duodenum are the parts most commonly affected (10).

Although the serosal form is less common than the other forms (2-40% of EG cases), it presents with clinical findings such as bloating and exudative ascites (2,15). Also, high eosinophil cell counts are observed in blood count (2). Eosinophilic acid has been reported more commonly in middle-aged women (1). However, it has also been reported in early infancy (30). It is usually diagnosed by laparoscopic examination and biopsy of the entire bowel wall (31). It responds well to steroids (31).

**DIAGNOSIS**

A history of food or drug allergies, atopic diseases, and family allergies are taken (8). It should be comprehensively evaluated by physical examination and subsequent laboratory evaluation (8).

Since EG is limited to small case series and single case reports in the literature, there are no specific diagnostic criteria (25). However, four main criteria are considered in the diagnosis: Presence of gastrointestinal symptoms, Eosinophilic infiltration of the gastrointestinal system, exclusion of other causes of intestinal eosinophilia (parasitic infections, side effects of drugs, inflammatory bowel disease (IBD), connective tissue diseases and lymphoproliferative malignancies) and involvement in other systems. not observed (10).

In cases where it is difficult to show an excess of eosinophilic infiltration in GIS, proof of the presence of eosinophil-rich ascites may be included instead of histological confirmation (32). Clinical history, laboratory results, endoscopy, and radiological findings are important for definitive diagnosis (10).

Because it is noninvasive and can be performed easily in clinical settings, it is frequently used in the diagnosis of peripheral blood eosinophilia, computed tomography or ultrasound (32).

**1. Laboratory Findings**

Peripheral eosinophilia is found in 20% to 80% of cases (32). Peripheral eosinophilia is significant when seen with GI symptoms. Peripheral eosinophilia is more significant in EG than in eosinophilic esophagitis (33). However, tests alone are not reliable and diagnostic (34).

Anomalies due to malabsorption may be observed in patients. Fat, protein and blood loss with feces; associated fat soluble vitamin deficiencies, hypoalbuminemia and iron deficiency anemia are seen (35). Patients with EG have high

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alpha1-antitrypsin in their stools (36). Protein loss may also result in low total immunoglobulin levels, but serum IgE may be elevated, which strongly supports the diagnosis of EG, along with other findings (37). However, although high IgE levels were found in the studies of Norihisa Ishimura et al, specific antigens were not detected (38). In 25% of cases, an increased erythrocyte sedimentation rate can be seen (35).

Stool examination should be performed to exclude parasitic infections (37).

**2. Radiological Findings**

Computed tomography (CT) scanning may show nodular and irregular thickening of the distal stomach and proximal small intestine (32), but these findings may also be present in other conditions such as Crohn's disease and lymphoma. In patients with muscle involvement, imaging may reveal bowel narrowing and reduction in lumen diameter, most commonly seen in the distal antrum or proximal small intestine (35). Ascites fluid is usually detected in patients with serosal involvement in ultrasonography.

**3. Endoscopy**

The endoscopic appearance in EG is not specific (32,37). It includes erythematous, fragile, nodular, and occasional ulcerative changes (37). There is a study stating that 5 out of 40 endoscopic biopsies missed eosinophilic infiltration (39).

The most common area with gastrointestinal lesion involvement was the small intestine (76.5%), followed by the colon (55.9%) and stomach (41.2%), and 26.5% had esophageal lesions (32).

When performing endoscopy, at least 6 biopsy specimens must be taken from normal and abnormal areas of the bowel to rule out the possibility of sampling error (40). In patients with esophageal or colonic symptoms, additional biopsy samples can be taken from relevant locations to aid diagnosis.

A relatively typical observation for EG is the presence of pseudopolyps (41). It can occur in up to 25% of patients.

The diagnosis can be confirmed by histopathological examination of gastric and duodenal biopsies. The gold standard for diagnosis is endoscopic biopsy showing prominent tissue eosinophilia (42). 80% of mucosal diseases are diagnosed by biopsy. The most accurate method is surgery, which provides a full-thickness sample for comprehensive pathology and facilitates the diagnosis of muscle and serosal EG (43). The study by Takashi Matsushita et al. Shows that race and environmental factors have little effect on eosinophil content, at least between Japan and Hawaii (43). Eosinophil infiltration in subepithelial tissues of the stomach and intestine can be found even in non-pathological conditions (43). Subepithelial eosinophil infiltration is different in each part of the gastrointestinal tract. Density increases from the stomach to the distal ileum, reaches a maximum in the terminal ileum and cecum, then begins to decrease until it reaches a very low level (44).

**DIFFERENTIAL DIAGNOSIS**

In the differential diagnosis, diseases involving the gastrointestinal system and associated with peripheral eosinophilia should be considered first. Laboratory findings, imaging modalities, endoscopic biopsies, and especially histopathological evaluation guide the correct diagnosis (45).

First of all in differential diagnosis; Intestinal parasitic infections (Ascaris, Strongyloides, Toxocara, Trichura, Trichinella, etc.), cow's milk allergy, protein-losing enteropathy, malignancies (lymphoma, stomach and colon cancer), inflammatory bowel diseases (especially Crohn's disease) and hypereosinophilic syndrome should be considered (45).

**TREATMENT**

There is no specific treatment algorithm for EG compared to EE (34). It should be kept in mind that 40% of patients will go into remission spontaneously during treatment (44).

**1. Diet Treatment**

The relationship between symptoms and food should be questioned in all patients, and those foods should be excluded from the diet if information is obtained. Six foods known to be very allergenic (soy, cereal, eggs, milk, nuts, seafood) should be excluded from the diet for at least six weeks (32,34). If control is not achieved with this method, elimination diet is applied (44). Peripheral eosinophilia is checked for evaluation of treatment after 4-6 weeks. A 50% reduction is considered a response to treatment. In patients without peripheral eosinophilia, endoscopic biopsies reduce eosinophilia and response to treatment is evaluated. If there is a response to the treatment, foods are added gradually with an interval of three weeks depending on the allergenicity.

It has been observed that 40–75% of pediatric patients go into remission with diet (44). It is particularly effective in children under 3 years of age (34,44). It should not be forgotten that the nutrition of children younger than 12 months may originate from cow's milk, since it is mainly obtained from milk (46). Clinical tolerance develops in 80% of patients up to the age of five (44). By using diet therapy alone, side effects of the steroid can be avoided (34,44).

## 2. Medical Treatment

### *2.1 Glucocorticoids*

If there is no response to the diet, glucocorticoids are used as the main treatment. Corticosteroids suppress gene transcription of IL3, IL4, IL5, GM-CSF and various chemokines (44). The use of local (budesonide) or systemic (prednisone) corticosteroids are the main components of therapy (22).

Glucocorticoids, which reduce the migration of neutrophils and decrease capillary permeability, reduce inflammation (45). As observed in case studies, clinical remission has been observed in 50-90% of the patients (7,25).

Prednisolone is started at 5–40 mg / day (25). Symptoms are reduced by 80% in one week. The eosinophil count returns to normal in 85.7% of them within two weeks. Prednisolone is tapered off within the following 2-3 weeks. In 20% of patients, longer treatment may be required or relapses may occur (46). In these cases, it is continued with a minimal dose that controls the symptoms.

Systemic steroids have a variety of side effects. Oral steroids such as budesonide that are not enteric coated can be used to avoid these side effects (36). Oscillation is not observed until the terminal ileum (36). Because of this feature, it should be preferred in patients involving the ileum and proximal colon (36). Budesonide, which is effective at a dose of 9 mg/day equivalent to 30-45 mg prednisolone, is used to induce and maintain clinical remission in patients (36,46). The initial budenoside of 9 mg/day can be reduced to 6 mg/day and then to 3 mg/day for maintenance therapy (44).

Both of the mentioned topical steroids reduce the intensity of inflammation. However, the duration of action is longer compared to systemic steroids. Conditions such as severe dysphagia, dehydration, weight loss and esophageal stricture are observed, as they act for an average of 4–12 weeks (47). In these situations, systemic steroids should be preferred first (47). In long-term treatment, the use of topical steroids should be preferred because of less side effects.

### *2.2 Immune suppressive agents*

Studies have shown that thiopurines (azothioprine or 6-mercaptopurine) can be used in steroid-dependent or steroid-resistant cases (44). Pancreatitis and leukopenia have been observed as the main serious adverse events (45).

### *2.3 Mast Cell Stabilizers*

Histamine, leukotrienes and other mediators; they inhibit the release of sensitized mast cells (37).

Sodium cromoglycate is administered in four doses of 800 mg / day (45). In addition to inhibiting cytokine release from mast cells, it also reduces antigenic absorption (44). There are no known side effects (45).

Ketotifen is an H1 antihistamine and mast cell stabilizer (40). Usage dose is 2x1 mg or 2x2 mg. Known side effects are fatigue and sleepiness (40).

### *2.4 Leukotriene Antagonists*

In a study conducted in a 38-year-old male with steroid-dependent EG, he was successfully treated with montelukast (44). Inhibits Leukotriene D4, an important cytokine in the inflammatory cascade. Although it cannot replace steroid therapy, it still appears to be a drug that can save steroids (44). The most common side effect is headache (45).

### *2.5 Anti-allergic Agents That Suppress Cytokine Production*

Suplatast tosilate is an important drug that suppresses the production of cytokines, especially IL-4 and IL-5, which are secreted from Th2 (44). Studies have shown that this drug may also be effective in the EG clinic (44).

### *2.6 Anti IL-5 Antibody (Mepolizumab, Reslizumab)*

In clinical studies, it was observed that after the use of mepolizumab, the level of eosinophils in the blood decreased by 75% and in the tissue by 50-70% (40). In another study, it was observed that Reslizumab significantly reduced blood and tissue eosinophil levels in 226 pediatric patients (44). However, it was found that the decrease in eosinophil levels of both treatment modalities did not correlate with clinical improvement (45).

### *2.7 Anti IgE Monoclonal Antibody*

In the Omalizumab drug study, which is a monoclonal antibody specific to IgE that is free-circulating, conducted in 9 patients with EG; It was found to decrease plasma eosinophil levels and improve the clinical picture of patients (44). Omalizumab was administered subcutaneously in the study (44).

### *2.8 Other Medical Treatments*

PPI (Proton pump inhibitor) group drugs that inhibit the expression of 'eotaxin-3 in esophageal cells can be used in the treatment of EE (44,45).
Research on eotaxin receptor (CCR3) blockade and monoclonal antibody of 'eotaxin-1 (bertilimumab) is ongoing (45).

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### 3. Surgical treatment

Studies suggest that surgical treatment should not be performed unless there is persistent pylorus or bowel obstruction (10,37).

## CONCLUSION

Eosinophilic gastroenteritis is a disease that damages the gastrointestinal wall by eosinophilic infiltration and degranulation (39). The fact that it is an eosinophilic disease and responds well to stereoid suggests that this disease is associated with a hypersensitivity reaction (37). However, mechanisms of IgE-dependent and delayed Th2 cell-mediated hypersensitivity are involved in the pathogenesis of eosinophilic gastroenteritis (44).

Eosinophilic gastroenteritis disease is still unknown and a multi-factorial disease. A clear clinical guideline has not been established so far. Corticosteroids play an important role in treatment. However, it is known that serious side effects occur in long-term use. Future studies will better explain the epidemiology and pathophysiology of EG.

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