

## Eosinophilic gastrointestinal disorders: Is the minimum age limit for eosinophilic gastrointestinal diseases lowering?

Eozinofilik gastrointestinal hastalıklar: Eozinofilik gastrointestinal hastalıkların görülme yaşı küçülüyor mu?

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*Eosinophilic gastrointestinal disorders constitute a pathology characterized by eosinophilic infiltration of the gastrointestinal tract, the symptoms of which vary depending on the affected digestive segments and the involvement of the different layers of the digestive wall. Eosinophilic gastrointestinal diseases include subcategories such as eosinophilic esophagitis, eosinophilic gastroenteritis and eosinophilic colitis, and depending on the localization of the eosinophilia, it is possible to group them as mucosal, serosal or muscular disease. Mucosal involvement is the most common. Patients with eosinophilic esophagitis suffer from nutrition intolerance, vomiting, and dysphagia; for patients with eosinophilic gastroenteritis, complaints are abdominal pain, diarrhea and blood in stool; and for patients with eosinophilic colitis, they are typically diarrhea and lower quadrant pain. The disease is typically observed in but not limited to the 3rd to 5th decades. The main therapeutic options include steroids and dietary modification. Between 2011 and 2012, 4 patients were diagnosed in our pediatric gastroenterology department. Two were diagnosed with eosinophilic esophagitis, one with eosinophilic colitis and one with eosinophilic proctocolitis. This study aimed to review eosinophilic gastrointestinal diseases in light of the recent studies, referring to children diagnosed with eosinophilic gastrointestinal disease.*

**Key words:** Children, eosinophilic, esophagitis, colitis

### INTRODUCTION

Gastrointestinal disorders (GIDs) involving an accumulation of eosinophils include a variety of conditions including classic immunoglobulin (Ig) E-mediated food allergy, inflammatory bowel disease, gastroesophageal reflux, and the primary eosinophilic gastrointestinal disorders (EGIDs) (eosinophilic esophagitis [EOE], eosinophilic gastroenteritis [EGE], eosinophilic colitis [EC], and eosinophilic proctocolitis [EPC]). EGIDs are an interesting yet somewhat poorly defined set of disorders that must include the infiltration of at least one layer of the GI tract with eosinophils, in the absence of other known causes for eosinophilia (e.g., parasitic infections or drug reactions). Peripheral eosinophilia is not required for the diagnosis,

*Eozinofilik gastrointestinal hastalıklar gastrointestinal kanalın eozinofilik infiltrasyonu ile karakterizedir. Hastalığın belirtileri etkilenen sindirim segmentine ve sindirim kanalının farklı tabakalarının tutulumuna bağlı olarak değişiklik gösterir. Eozinofilik gastrointestinal hastalıklar, eozinofilik özofajit, eozinofilik gastroenterit ve eozinofilik kolit gibi alt gruplara ayrılır. Eozinofilinin yerleşimine bağlı olarak mukozal, serozal ya da müküler hastalık olarak gruplamak mümkündür. Mukozal hastalıklar bunların arasında en yaygın olanıdır. Eozinofilik özofajitli hastalar hazımsızlık, kusma, disfaji şikayetleri gösterirken, eozinofilik gastroenterit hastaları karın ağrısı, ishal ve kanlı dışkılama şikayetlerine sahiptir. Eozinofilik kolitli hastalarda ise tipik olarak ishal ve alt kadran ağrısı şikayetlerine rastlanır. Hastalık tipik olarak 3. ve 5. dekatlarda görülmekle birlikte diğer yaş gruplarında da görülebilir. Ana tedavi seçenekleri arasında steroid ve diyet değişikliği vardır. 2011 ile 2012 yılları arasında çocuk gastroenteroloji bölümümüzde 4 hastaya eozinofilik gastrointestinal hastalık tanısı konuldu. Bunlardan 2 tanesi eozinofilik özofajit, 1 tanesi eozinofilik kolit, diğeri ise eozinofilik proktokolit tanısı aldı. Bu makalede eozinofilik gastrointestinal hastalık tanısı almış çocuk hastalarımız güncel çalışmalar ışığında gözden geçirildi.*

**Anahtar kelimeler:** Çocuklar, eozinofilik, özofajit, kolit

although it is a frequent finding. First described in 1937 by Kaijser, interest in EGIDs has grown in recent years in parallel with an increasing number of case reports and case series from different continents (1,2).

### CASE REPORTS

#### Case 1

An eight-year-old female patient applied to the clinic with the diagnosis of gastroesophageal reflux. Despite using various medicines for reflux, there was no improvement in the patient's complaints. The patient's medical history did not reveal the disease; however, her family history

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indicated that the mother had allergic rhinoconjunctivitis. Growth monitoring of the patient as well as the physical examination were normal. Complete blood count revealed moderate eosinophilia (1800/mm<sup>3</sup>). IgE, food mix and Phadiatop tests were in normal ranges. No parasites were seen in the stool sample. An upper GI endoscopy demonstrated esophageal mucosal edema, and through the esophageal lumen, esophageal vertical linear furrows were shown (Figure 1).

Biopsies from different parts of the esophagus showed a dense eosinophilic infiltrate [ $>25$  eosinophils per high power field (HPF)] (Figure 2). The patient was diagnosed with EOE and treated with fluticasone 125 mcg inhaler, two puffs swallowed three times a day for six weeks. Her reflux symptoms resolved.

### Case 2

A six-year-old male patient applied to the clinic with the complaint of vomiting, non-responsive to anti-reflux medicines. According to the patient's history, he had been diagnosed with acute urticaria, and had been started on antihistaminic medicine and proton pump inhibitor for the vomiting. The family history was unremarkable, and the physical growth of the patient was within normal ranges. The hemogram showed moderate eosinophilia (2100/mm<sup>3</sup>). Food mix and Phadiatop allergy tests were normal, and specific IgE was negative. There were no parasites in the stool sample and the esophagogram was normal.

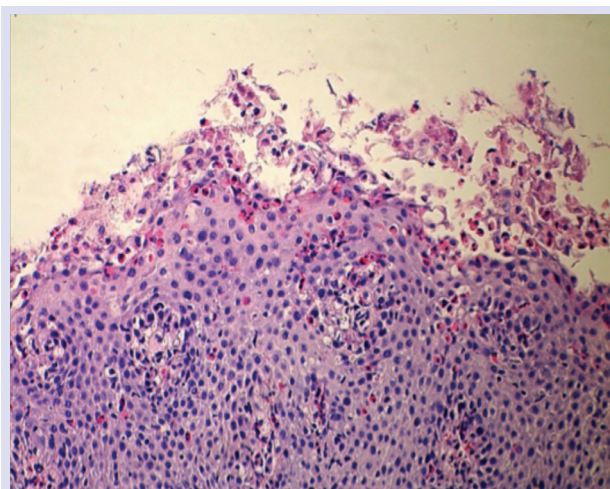
Upper GI endoscopy revealed the presence of mucosal edema and concentric rings along the entire length of the esophagus (Figure 3). Biopsies from proximal and distal parts of the esophagus showed eosinophilic infiltration ( $>25$  eosinophils per HPF), and EOE was diagnosed. He was started on fluticasone 125 mcg inhaler, two puffs swallowed three times a day for six weeks. His vomiting and reflux symptoms resolved.

### Case 3

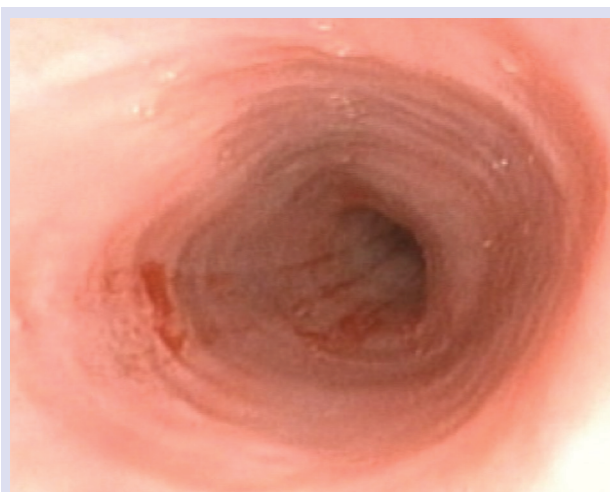
A three-year-old female admitted with complaints of diarrhea and inability to gain weight. The complaints had been ongoing for almost three months. The patient and family histories were unremarkable. The height of the patient was normal (95 cm) for her age, but her weight was within 3-10 percentile (11.3 kg). The physical examination revealed obtained subcutaneous fat and bowel sounds on auscultation. Complete blood count showed anemia (10 g/dl) and moderate eosinophilia (1600/mm<sup>3</sup>). Biochemical tests and sedimentation rate were within normal ranges. Serum antiendomysial antibodies (EMA) were negative, and serum IgA and IgE were in the normal ranges. The stool sample of the patient



**Figure 1.** Appearance of eosinophilic esophagitis: Vertical linear furrows are demonstrated.



**Figure 2.** Non-keratinized multi-layered squamous epithelium of the esophageal mucosa. Severe eosinophil infiltration within the epithelia reached the upper layers (hematoxylin & eosin [H-E] stain).



**Figure 3.** Mucosal edema and concentric rings along the entire length of the esophagus are seen.

revealed no parasites. Stool fat reductants were negative. Colonoscopy revealed patchy areas, erythema, and reduced submucosal vascularity (Figure 4). Biopsies from the colon showed a dense eosinophilic infiltrate (Figure 5). The patient was diagnosed with EC and treated with leukotriene antagonist 4 mg perorally, once a day for 12 weeks. Her diarrhea resolved with this treatment.

#### Case 4

A one-year-old female applied to the clinic with rectal bleeding. The patient and family history were unremarkable. The patient had been fed by breast milk and supplementary nutrition. The height and weight of the patient were normal. Complete blood count showed hemoglobin 12 g/dl, thrombocytes 250000/mm<sup>3</sup>, and moderate eosinophilia (1700/mm<sup>3</sup>). Sedimentation rate and prothrombin time (PT) – partial thromboplastin time (PTT) were normal. Stool occult blood was positive, stool microscopy revealed abundant leukocytes, and stool culture examination was normal.

The biopsy of the rectum and sigmoid colon revealed eosinophil infiltration (30 to 40/HPF) of the lamina propria and intraepithelial and lymphoid nodular hyperplasia of the submucosa. Allergy skin tests were negative. The patient was diagnosed with EPC. Elimination of the offending protein from the diet, through the use of an extensively hydrolyzed protein-based formula, led to clinical resolution of the bleeding in two weeks.

## DISCUSSION

Although first described in the 1930s, EGIDs did not attract great attention until the last decade. Eosinophilic disorders of the GI tract can be separated into primary or secondary eosinophilic diseases: primary having no inciting cause and secondary due to other diseases resulting in eosinophilia (3).

The exact incidence and prevalence of the primary eosinophilic disorders of the GI tract (EOE, EGE, EC, EPC) are variable for each type of GI disorder. These diseases are occurring or being diagnosed with increasing frequency in both pediatric and adult populations and are especially prominent in pediatric populations (4). The best-documented and most-studied EGID is EOE. In adults, it occurs most commonly in the 30s and 40s. There is a male predominance, with a 3:1 male to female ratio, and the incidence of EOE may be as high as 1:1000 individuals (5,6).

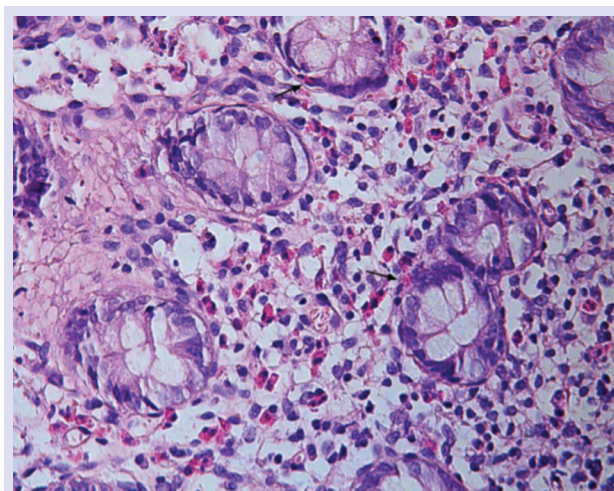
Eosinophilic esophagitis (EOE) can present at any age with a diverse range of symptoms, including regurgitation, vomiting, abdominal pain, food refusal, weight loss,

dysphagia, or food bolus impaction. Adult patients often present with dysphagia, food impaction, or reflux symptoms non-responsive to proton pump inhibitor therapy (7). In this study, the patients with EOE applied to our clinic with intractable reflux (non-responsive to proton pump inhibitor therapy).

Clinical features of EGE may reflect the extent, location and depth of infiltration of this eosinophilic inflammatory process within the GI tract. Abdominal pain and diarrhea are common. Weight loss may occur, in part related to malabsorption. If muscular layers are involved, obstruction or even acute abdomen has been recorded, while serosal involvement may be associated with evidence of ascites (8).



**Figure 4.** Appearance of eosinophilic colitis, with patchy areas of erythema on mucosal layers as well as reduced submucosal vascularity.



**Figure 5.** Intense eosinophilic leukocyte infiltration is seen on lamina propria in the colon. Eosinophils attacked the epithelia of some crypts (H-E x200).



Eosinophilic colitis (EC) has a bimodal age distribution affecting infants and young adults. Clinical manifestations of EC depend mainly on the colonic layers affected by the eosinophilic infiltration. Mucosa-predominant EC, the most common form, is associated with mucosal injury and presents with malabsorption and diarrhea. Transmural disease presents with colonic wall thickening and features of acute intestinal obstruction. Serosal disease, a rare form, presents with ascites (9).

Eosinophilic proctocolitis (EPC), also known as allergic proctocolitis (AP), has been recognized as one of the most common etiologies of rectal bleeding in infants. In this study, a patient diagnosed with EC had chronic diarrhea and a patient diagnosed with EPC had rectal bleeding.

Diagnosis of EGIDs requires a high index of suspicion, as the symptoms and presentations are nonspecific. Evaluation for EGIDs should be performed in all patients with intractable symptoms (dysphagia, abdominal pain, bloating, diarrhea, weight loss, dysphagia, and vomiting), especially in individuals with a strong history of allergic diseases, with or without peripheral blood eosinophilia and/or a family history of EGIDs (10).

The definite diagnosis requires the existence of eosinophilia on the samples taken from the GI wall biopsy. Multiple samples are required for the diagnosis (11). The number and location of eosinophils are useful when trying to differentiate EOE from gastroesophageal reflux disease (GERD). Up to 7 eosinophils/HPF (400x) is most indicative of GERD, whereas more than 20-24 eosinophils/HPF is characteristic of erosive esophagitis (EE) (3,22). Both EC and EPC are characterized by infiltration of >30 eosinophils per HPF (13,14).

Endoscopic features of EOE are esophageal linear creases oriented longitudinally (furling). Endoscopic studies have shown mucosal rings, strictures, ulcerations, whitish papules, and polyps in EOE. Micronodules are noted in EGE, and these lesions often contain marked aggregates of lymphocytes and eosinophils. On endoscopic examination of patients with EC, patchy erythema, loss of vascularity, and lymphonodular hyperplasia are seen typically localized to the rectum, but may extend to the entire colon (4,15). Upper endoscopy of the patients with EOE showed esophageal mucosal edema, vertical linear furrows and concentric rings. Biopsies from different parts of the esophagus showed a dense eosinophilic infiltrate. The patients with EC and EPC had patchy areas of erythema on mucosal layers as well as reduced submucosal vascularity. Biopsies from the colon showed an eosinophilic infiltrate.

The majority of patients with EGIDs have increased total

IgE levels and a history of other atopic diseases, including asthma, eczema, or allergic rhinitis. Most also have positive food-specific IgE levels and positive skin tests to food allergens. The most common foods reported in EGIDs are eggs, milk, and fish, and there are many other food particles related to development of EGIDs (16). Peripheral blood eosinophilia is noted in about two-thirds of patients with EGE and may be found in patients with EC (17,18). The patients in this study had a medium peripheral eosinophilia. Serum IgE levels were within normal ranges. There were no parasites on stool samples, and allergy tests were negative. This is likely due to a decrease in sensitivity of the patient depending on age.

The differential diagnosis of EGIDs includes parasitic infections, inflammatory bowel disease, connective tissue diseases, some malignancies, and adverse effects of drugs. They have been strongly associated with food allergies, and atopic diseases or a family history of allergies has been elicited in about 70% of cases (19).

Patients with EGIDs have two primary treatment options, broadly represented as either dietary or medicine-based therapies. Dietary restriction with either an elemental or elimination diet has been very successful in children, with reported response rates up to 98%. Dietary studies in adults are limited, appearing only as abstracts. Corticosteroids have been used successfully to treat EGIDs in both children and adults (12). Swallowed fluticasone, budesonide and ciclesonide are effective especially in EOE (20,21). In severe cases, refractory or dependent on glucocorticoid therapy, the alternatives are intravenous alimentation or immunosuppressive antimetabolite therapy (azathioprine or 6-mercaptopurine) alternatives (22). Other treatments (antihistamines, cromolyn, leukotriene antagonist, mepolizumab) for EGIDs have been examined. However, there is little information in the literature on the effectiveness of these drugs (23). The cases with EOE had recessed reflux complaints after the oral fluticasone treatment. Diarrhea of the patient with EC was cured after montelukast treatment. The EPC case was cured with elimination diet.

This rising prevalence of EGIDs and allergic diseases in general has occurred in parallel with a decrease in infectious diseases, a causal event that has been explained through the hygienic hypothesis. This hypothesis brings an imbalance to the immune system and a splay for developing allergic and autoimmune disorders triggered by altered or missing innate immune cell activation (13,24,25). EGIDs have captured the interest of many gastroenterologists worldwide. In spite of the increased interest, very few data are available on the prevalence of this disease in

the pediatric population. Fox et al. have found that 6% of their pediatric patients had EOE, whereas Liacouras et al. reported that 1% of their patients with esophagitis had EOE (4). The increasing incidence of EOE is paralleled by rising routine esophageal biopsy rates in symptomatic patients on a population basis (26). Except for EOE, available data about the epidemiology of EGIDs in general and EGE in particular are limited. A recent report from the United States suggests that EGE or colitis was estimated to have an overall prevalence of 28 per 100,000 (13). Kim et al. (27) reported 31 new cases of EGE in Seoul, Korea between January 1970 and July 2003. Chen et al. (28) reported 15 patients, including 2 children, with EGE who were evaluated over an 18-year period in a hospital in China in 2003. Venkataraman et al. (29) reported 7 new diagnoses of EGE over a 10-year period in India. Although male predominance is common in EGIDs in the adult population, our Pediatric Gastroenterology Depart-

ment described 4 patients; 2 patients with EOE, 1 with EC and 1 with EPC. Three of the patients were females and one was a male, and their average age was 4 years and 6 months.

In conclusion, EGIDs are characterized by rare eosinophilic inflammation. EGIDs should be considered in patients with GI system-related findings, personal or familial atopy anamnesis and in cases such as when nutrition and clinical findings are related. Although the diseases are typical to the 3rd and 5th decades and more common among males, children are also affected. Appearance of EGIDs at an earlier age may depend on environmental factors, genetic predispositions, aeroallergens, or eating habits. More studies are required regarding the cause of the EGIDs in children. Since endoscopic methods are being used more commonly, the number of reported cases both within and outside Turkey is increasing.

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