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The first experience of eosinophilic esophagitis in Turkish children

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Background/aims: *Eosinophilic esophagitis is a rare allergic disease of the esophagus with no published data in Turkish children.* ***Methods:*** *This is an observational study of children diagnosed as eosinophilic esophagitis in our hospital between February 2009 and January 2011. We retrospectively analyzed the clinical features, allergic work-up, endoscopic and histological findings, and response to treatment.* ***Results:*** *We followed seven patients in this period with a histopathologic diagnosis of eosinophilic esophagitis. The mean age at diagnosis was 5.05±2.97 years (range: 1-9 years), and four of them were male. The most frequent symptom was gastroesophageal reflux disease-like symptoms (vomiting, regurgitation, and heartburn) (42.9%). Peripheral eosinophilia and high serum total IgE levels were found in four patients (57.2%). Sensitization to food (71.4%) was more frequent than that of aeroallergens (28.6%). Endoscopic findings suggestive of eosinophilic esophagitis were present in four patients (57.2%). Comorbid allergic disease was present in five patients (71.4%). All patients were treated by elimination diet (85.7%) and/or inhaled corticosteroid treatment (71.4%). The mean follow-up period was 12.4±6.1 months (range: 6-24 months). All but one patient showed complete clinical response to their treatment. No significant side effect was observed during the follow-up period.* ***Conclusions:*** *Eosinophilic esophagitis is a rare gastrointestinal allergic disorder frequently comorbid with other allergic diseases and with different manifestations and response profiles to treatment modalities.*

Key words: Children, eosinophilic esophagitis, follow-up, treatment

Türk çocuklarında eozinofilik özofajit: İlk deneyim

Amaç: *Eozinofilik özofajit özofagusun nadir görülen allerjik hastalığıdır. Şu zamana kadar Türk çocuklarında eozinofilik özofajit ile ilgili yayınlanmış bir bildiri bulunmamaktadır.* ***Yöntem:*** *Bu gözlemsel çalışmada eozinofilik özofajit tanısıyla hastanemizde Şubat 2009 ile Ocak 2011 tarihleri arasında izlediğimiz çocuk hastaların klinik özellikleri, endoskopik ve histopatolojik bulguları, allerjik değerlendirmeleri ve tedavi cevapları retrospektif olarak incelenmiştir.* ***Bulgular:*** *İki yıllık süre içinde histopatolojik olarak eozinofilik özofajit tanısı koyduğumuz yedi çocuk olgu izlenmiştir. Olguların ortalama yaşı 5.05±2.97 yıl (aralık; 1-9 yıl) olup dördü erkekti. Gastroözofageal reflü semptomları (kusma, rejürjitasyon, göğüste yanma) en sık görülen başvuru şikayetiydi (42.9%). Periferik eozinofili ve serum total IgE yüksekliği dörder hastada saptandı (57.2%). Besin duyarlılığı (71.4%), aeroallerjen duyarlılığına (28.6%) göre daha sık oranda bulundu. Dört hastada eozinofilik özofajit tanısını destekleyen endoskopik bulgular da mevcuttu (57.2%). Beş hastada ko-morbid allerjik hastalık vardı (71.4%). Hastaların tamamı eliminasyon diyeti (85.7%) ve/veya inhale kortrikosteroidle (71.4%) tedavi edildi. Ortalama izlem süresi 12.4±6.1 ay (aralık: 6-24 ay) idi. Biri hariç tüm hastalarda verilen tedaviye tam klinik yanıt alındı ve önemli bir yan etki gözlenmedi.* ***Sonuç:*** *Eozinofilik özofajit sıklıkla ko-morbid allerjik hastalıkların eşlik ettiği, tedavilere verilen yanıtın ve klinik bulguların farklılıklar gösterebildiği nadir görülen bir allerjik gastrointestinal sistem hastalığıdır.*

Anahtar kelimeler: Çocuk, eozinofilik özofajit, klinik izlem, tedavi

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by dense tissue eosinophilia (1). Most of the studies document a rising prevalence of this disorder, but

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it is unclear whether this is due to better awareness of the disease by physicians or to a truly rising incidence (2). The pathogenesis of EoE remains unclear; however, there is growing literature supporting the role of food and aeroallergens (3). EoE is closely associated with other allergic diseases, such as food allergy, bronchial asthma and atopic eczema, especially in the pediatric population (1). The presenting symptoms of EoE vary depending on the age of the patients. While infants and young children present with feeding problems and gastroesophageal reflux disease (GERD)-like symptoms (vomiting, regurgitation, and heartburn), school-age children and adolescents often behave as adults and present with abdominal pain, dysphagia and/or food impactions (4). At present, there is no standardized treatment strategy for EoE (1,4). Although a few studies suggest potential progression of untreated patients, the natural history of EoE is largely unknown (1,4-6).

To our knowledge, EoE was reported only in adults in our country. Here, we present the first Turkish pediatric case series that investigated the demographic, clinical, endoscopic and histological findings, and response to treatment.

MATERIALS AND METHODS

This retrospective analysis included children who were diagnosed as EoE at our hospital between February 2009 and January 2011. All patients were initially admitted to the Department of Pediatric Gastroenterology with various gastrointestinal (GI) symptoms necessitating upper GI endoscopy for diagnosis. Diagnosis of EoE was done histopathologically based on >15 eosinophils per high-power field (hpf) in the esophagus along with the absence of eosinophilic inflammation in the stomach and duodenal biopsies. All patients were consulted for allergic work-up and management to the Department of Pediatric Allergy and Asthma in the same hospital. A detailed personal and family history about GI and allergic symptoms for comorbid allergic diseases, such as allergic rhinitis, asthma, atopic eczema, and food allergy, was taken. Sensitization to common and suspected food allergens in the history was investigated by skin prick tests (SPT), specific IgE levels in serum, and atopy patch tests (APT), while sensitization to aeroallergens was determined only by SPT. Serum total IgE levels and peripheral eosinophil percentage were measured in all patients. Esophageal biopsy specimens were further evaluated for other common histopathological features of EoE besides absolute eosinophil count per hpf. We analyzed the patients' medical records for details regarding demographic information, clinical presentation, laboratory data, endoscopic and histological findings, and the response to treatment in the follow-up period.

Statistical Analysis

Statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Whereas the metric discrete variables were shown as mean ± SD, the number of cases and percentages were used for nominal data.

RESULTS

Four of seven patients (57%) with EoE were male. The age of the patients ranged from 1.5 to 11 years old. The mean age at onset of symptoms and at diagnosis was 2.57±2.29 years and 5.05±2.97 years, respectively. The mean delay to the diagnosis of EoE was 2.50±1.15 years. Six patients (85.7%) were diagnosed as GERD refractory to adequate PPI (proton pump inhibitor) therapy before upper GI endoscopy. None of the patients had family history of EoE. In these patients, 3 (42.9%) had GERD-like symptoms, 2 (28.6%) had abdominal pain, 1 (14.3%) had dysphagia/food impaction, and 1 (14.3%) had feeding problems (Table 1).

A total of 5 patients (71.4%) had concomitant allergic disease, which consisted of asthma in 4 patients, allergic rhinitis in 2 patients, atopic eczema in 1 patient, and food-induced anaphylaxis in 1 patient. SPT and APT were performed in all patients, while specific IgE antibodies in serum could be measured in only 3 patients. SPT and APT were found positive in 5 (71.4%) and 3 (42.9%) patients, respectively. Five patients had food sensitization, 2 of whom also had aeroallergen sensitization on SPT. Egg was the most common food allergen, found in 4 patients (57.2%), followed by cow's milk in 3 patients (42.9%) (Table 1). Peripheral eosinophilia and high serum total IgE levels were found in 4 patients (57.2%).

Endoscopic abnormalities were found in 4 patients (57.2%) (Figure 1). These abnormalities included linear furrowing in 3 patients (42.9%), white exudates in 2 patients (28.6%), esophageal trachealization in 1 patient (14.3%), and esophageal narrowing in 1 patient (14.3%). In 3 patients (42.9%), endoscopy was normal (Table 2).

Table 1. Demographic and clinical characteristics of EoE cases

Number	Gender	Age (years)	Age at diagnosis (years)	Age at onset of symptoms of EoE (months)	Symptoms	Associated allergic diseases	Skin prick tests	Serum specific IgE	Atopy patch test	Serum total IgE level (IU/mL)	Peripheral eosinophil percentage (%)
1	F	1.5	1.0	6	Feeding problems	Anaphylaxis (cow's milk)	Cow's milk	NA	Cow's milk and egg	18	0.7
2	F	3.5	2.5	24	GERD-like symptoms	Asthma, atopic eczema	Egg	Positive (cow's milk, egg)	Negative	194	9.4
3	M	4.5	3.5	30	GERD-like symptoms	None	Negative	Negative	Negative	8.9	3.1
4	M	5.5	4.5	42	GERD-like symptoms	None	Negative	Negative	Negative	44.4	1.0
5	F	8.5	7.5	24	Abdominal pain	Asthma	Cacao	NA	Cacao	197	16.2
6	M	9.0	7.5	36	Abdominal pain	Asthma, allergic rhinitis	Egg, wheat, peanut, walnut, hazelnut, almond, cereals, soybean, kiwi, pollens and dust mite	NA	Walnut and hazelnut	324	6.6
7	M	11.0	9.0	48	Dysphagia / Food impaction	Asthma, allergic rhinitis	Egg, cow's milk, hazelnut, black pepper, pollens, cockroach	NA	Negative	602	10.5

EoE: Eosinophilic esophagitis. NA: Not available. GERD-like symptoms: Vomiting, regurgitation, and/or heartburn.

Mean eosinophil count was 45.7 eosinophils/hpf (range: 25-80/ hpf). Eosinophil clusters (micro-abscess formation), eosinophilic degranulation, superficial eosinophilic density, and papilla elongation were detected in 6 of 7 patients (85.7%) (Figure 2). Intercellular edema was observed in 3 patients (42.9%). Fibrosis in the lamina propria could be evaluated in 3 patients and was present in 2 of them (Table 2).

All patients were treated by elimination diet and/or inhaled corticosteroid treatment. Elimination diet was given in 6 patients (85.7%). Elimination diet therapy included allergen-specific diet based on the results of SPT and APT in 3 patients, six-food elimination diet in 2 patients, and amino-acid based elemental diet in 1 patient. Two patients received only elimination diet therapy. Four patients were treated with a combination of elimi-

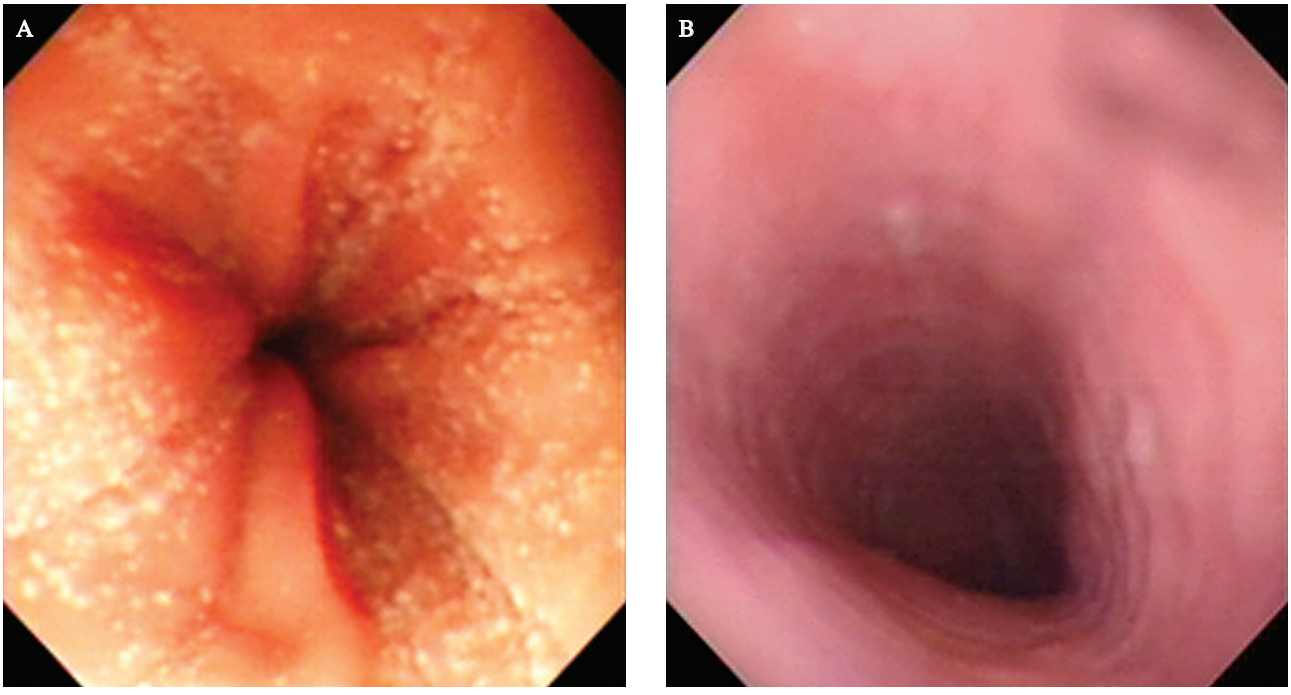

Figure 1. Endoscopic findings in our patients with EoE: **A)** white exudates (Patient 7); and **B)** esophageal trachealization (Patient 1).

Table 2. Endoscopic and histological findings and treatment outcomes of EoE cases

Number	Endoscopic Findings					Histological Findings						Treatment Outcomes		
	Linear furrows	White exudates	Esophageal trachealization	Esophageal narrowing	Peak eosinophil counts /hpf	Eosinophil clusters (micro-abscess)	Superficial eosinophilic density	Papilla elongation	Eosinophil degranulation	Intercellular edema	Fibrosis of lamina propria	Follow-up period (months)	Therapy	Clinical response
1	+	-	+	-	50	+	+	+	+	-	-	6	Diet	Complete response
2	-	-	-	-	80	+	+	+	+	-	NA	12	Diet + Topical CS	Complete response
3	+	-	-	-	60	+	+	+	+	+	NA	12	Diet + Topical CS	Partial response
4	-	-	-	-	25	-	-	+	+	-	NA	12	Topical CS	Complete response
5	-	+	-	-	35	+	+	+	+	+	+	12	Diet + Topical CS	Complete response
6	-	-	-	-	25	+	+	-	+	-	+	18	Diet + Topical CS	Complete response
7	+	+	-	+	55	+	+	+	-	+	NA	24	Diet	Complete response

EoE: Eosinophilic esophagitis. CS: Corticosteroid. NA: Not available. +: Observed. -: Not observed.

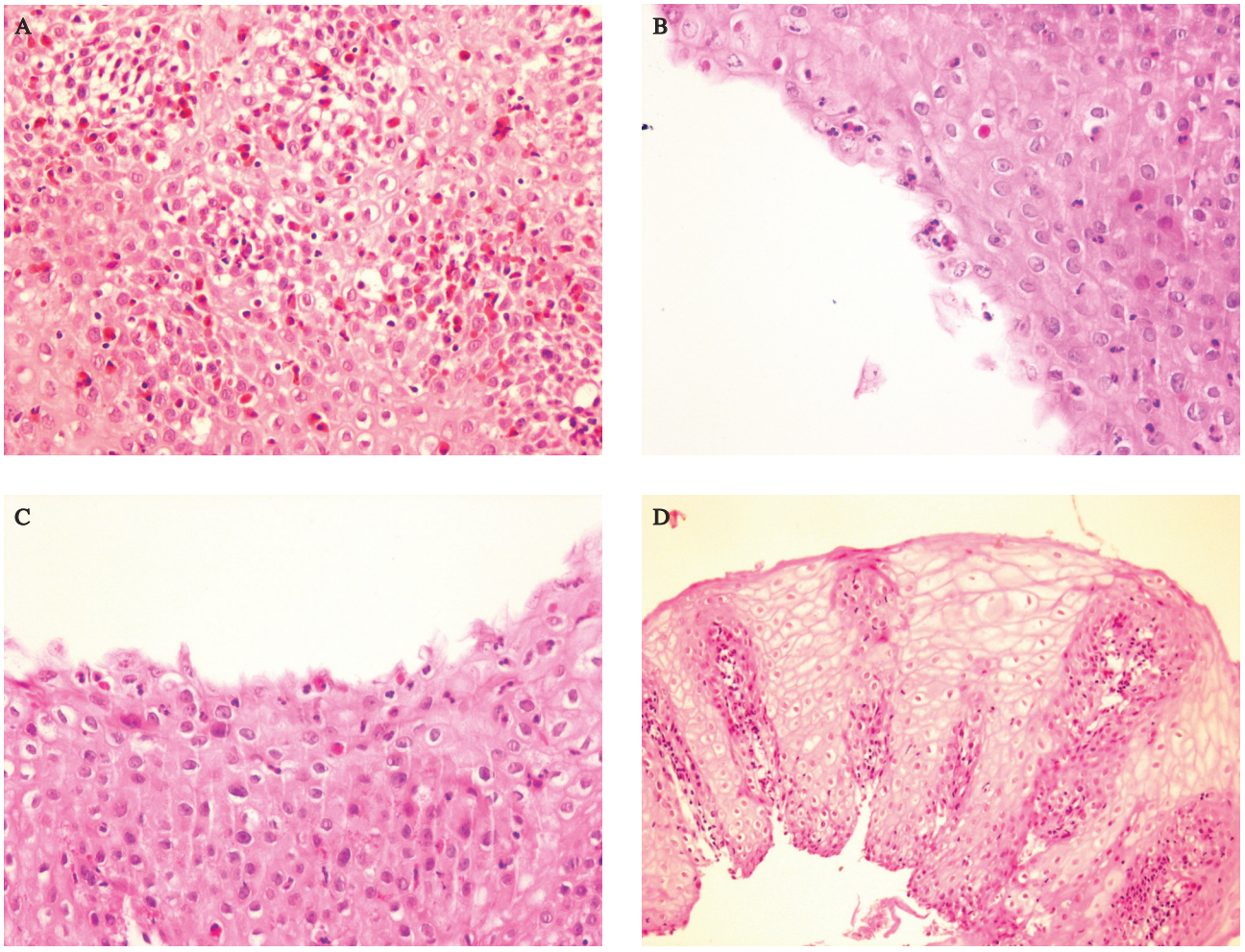

Figure 2. Histologic findings in our patients with EoE (H&E, original magnification x 400): **A)** dense eosinophilic infiltration (Patient 5); **B)** eosinophil clusters (micro-abscess) (Patient 6); **C)** superficial distribution of eosinophils (Patient 2); and **D)** papilla elongation (Patient 3).

nation diet and swallowed viscous inhaled corticosteroid. One patient, who was non-atopic, was treated only with swallowed viscous inhaled corticosteroid (Table 2). Patients swallowed viscous budesonide form (Pulmicort® 0.5 mg/ml nebules, Astra Zeneca R&D) twice per day. After administra-

tion, patients neither ate nor drank for 30 minutes. The dose of swallowed budesonide was halved in patients who remained asymptomatic for at least 3 months. Patients were followed in 3-month intervals if not indicated otherwise. The mean follow-up period in our patients was 12.4±6.1 months (range: 6-24 months). All but 1 patient showed complete clinical response to their treatment (Table 2).

DISCUSSION

This is the first report of a pediatric EoE case series from Turkey. Here, we describe the demographic, clinical, endoscopic, and histological features, treatment outcome, and follow-up of seven children with EoE.

The exact etiology and pathogenesis of EoE are not well-understood (2-4). The majority of EoE patients have evidence of food and aeroallergen hypersensitivity and other concurrent allergic diseases (6,7). Experimental and clinical studies suggested both T helper type 2 (Th2)-mediated humoral (type I hypersensitivity) and cellular (type IV hypersensitivity) mechanisms in the immunopathogenesis of EoE (8). However, not all patients demonstrate evidence of type I (SPT and specific IgE measurements in serum) and type IV (APT) hypersensitivity (9,10). In our study, five patients showed hypersensitivity to food with SPT and/or specific IgE in serum, and three of them also had positive APT with the same food allergens. None of our patients was found to have positive APT and negative SPT and/or serum specific IgE to food. Our cases also had a high rate of food sensitization (71.4%) and associated allergic diseases (71.4%). Asthma was the most common allergic disease in our cases, supporting the role of allergy in the EoE etiology. In addition, although the majority of EoE patients have evidence of food hypersensitivity, only a subset (10-30%) has a history of anaphylaxis with food (6,11). Similarly, the youngest child (Patient 1) in our group also had a history of anaphylaxis to cow's milk (submitted as a case report).

Clinical complaints have a highly variable spectrum in EoE patients depending on age. Younger children usually present with feeding problems and GERD-like symptoms, whereas abdominal pain, dysphagia and food impactions are the most common symptoms in school-age children and adolescents (11,12). Because most of our cases were young, preschool-age children, GERD-like symptoms and feeding problems were the most common complaints. A typical adult symptom of EoE, food impaction, was seen in one patient in our group (Patient 7). It is suggested that the variation in symptoms may be due to differences in the ability of different age groups to enunciate discomfort or may represent different stages of the disease.

Because none of the complaints are specific for EoE, delay in diagnosis is frequent and reported to be as long as 4.5 years (13). In our series, the mean delay in diagnosis was 2.5 years. Due to the clinical similarity between GERD and EoE, all but one case had been treated several times with PPI before being admitted to our hospital (14). None of these cases had responded to PPI therapy. EoE should be considered in case of GERD-like symptoms unresponsive to PPI treatment.

Upper endoscopy is the first diagnostic step in the evaluation of an individual with suspected EoE. Longitudinal furrowing, white exudates, esophageal trachealization, esophageal narrowing and strictures, Schatzki ring, and friability/crepe paper mucosa are endoscopic signs suggesting EoE, although they are not pathognomonic (1). However, Potter et al. (15) commented that if a patient has both esophageal narrowing and trachealization, physicians should strongly suspect a diagnosis of EoE. On the other hand, normal endoscopy may be observed in 26% to 32% of children with EoE (16,17). In our series, four patients (57.2%) had abnormal endoscopic findings, with linear furrowing being the most common.

The number of intraepithelial eosinophils in esophageal biopsy specimens is the main diagnostic criterion for EoE. The American Gastrointestinal Association (AGA) first released a consensus statement on the diagnosis and management of EoE in 2007 and updated it recently in 2011. They recommended using >15 eosinophils in any hpf as a diagnostic criterion for EoE (1). A recent review also described "major" and "minor" histologic features associated with EoE, which may distinguish it from other entities, especially GERD. In this review, epithelial eosinophilia (>15/hpf), eosinophilic micro-abscess and superficial eosinophilic density are described as major, while papilla elongation, basal cell hyperplasia, intercellular edema, and an increase in other inflammatory cells are introduced as minor histopathologic features (18). All our cases had >15/hpf intraepithelial eosinophilia in esophageal specimens. In addition, six of seven patients also had other major histologic features.

Among the minor histologic features, papilla elongation and intercellular edema were found in 85.7% and 42.9% of our patients, respectively. Due to the patchy distribution of the eosinophilic infiltration, the biopsies should be taken from several locations to maximize diagnostic yield (1). One previous report demonstrated that five biopsies increased the sensitivity of diagnosis of EE to 100% (19). In our EoE cases, a minimum of 3 and maximum of 5 esophageal biopsies had been taken.

There is no consensus regarding the treatment of EE. However, current treatment strategies include elimination diet and medical management with topical or systemic corticosteroids. Endoscopic dilatation is applied when strictures are present (1,4). Elimination diet may be given in three forms: an elemental diet (amino-acid-based formula) or specific allergic food (determined by SPT and/or APT) elimination diet, or six-food (milk, egg, wheat, nuts, fish, soya) elimination diet. All types of elimination diets are effective in the treatment of EoE (9,20,21). Therefore, we also explained the types and the importance of the elimination diet and recommended it as the first-line treatment to all of our patients. All but one accepted the diet. Elimination diet in the form of elemental formula is difficult to comply with in the long-term particularly in children, adolescents and adults, as well as being expensive. Two of our patients (Patients 1 and 7) showed complete clinical response with elimination diet alone. One of them was our youngest patient (Patient 1) in whom we were able to use elemental formula. Our other patient (Patient 7), who also improved with diet alone, used specific food elimination diet. All our patients treated with elimination diet were provided nutritional support by a professional dietician. One of our patients did not want to use either elemental or six-food diet (Patient 4). Swallowed budesonide was added to the treatment in this patient, and in other patients who did not improve with (Patients 2, 5 and 6) or adhere to (Patient 3) elimination diets. Patient 3 was receiving the six-food elimination diet because the child did not want to use elemental formula. However, the parents of this patient were also unable to adhere to this diet. Therefore, this patient gave up the six-food diet during the follow-up and continued with swallowed budesonide treatment. The frequency of his most bothersome symptom (vomiting) reduced, but an asymptomatic period could not be achieved. Thus, other causes of persistent tissue eosinophilia were investigated further, and an upper GI endoscopy and biopsy were repeated in this patient. Oral methylprednisolone treatment (1 mg/kg/d) was added to his treatment because of persistent eosinophilia (80 eosinophils/hpf) in the second biopsy specimens.

Topical inhaled corticosteroids may be used as an add-on treatment or as an alternative to elimination diet in EoE (1,2,4). Budesonide or fluticasone dipropionate are the common topical inhaled corticosteroids used in EoE treatment (1,4). Topical inhaled corticosteroids are popular because they are easy to use, have few side effects and impact less on quality of life than does an elimination diet. However, there are only two randomized placebo-controlled studies on the use of topical inhaled corticosteroids, one with swallowed budesonide (1000-2000 µg/day) and one with fluticasone propionate spray (880 µg/day) in children with EoE (22,23). Both studies used topical corticosteroid for three months and demonstrated significant histological and clinical response compared to the placebo arm. Similarly, we used swallowed budesonide with a starting dose of 2000 µg/day in our patients. The data on the long-term efficacy of inhaled corticosteroids is also very limited. To date, there has been only one adult randomized, placebo-controlled trial evaluating the efficiency and safety of long-term topical corticosteroid in EoE patients (24). That study demonstrated that 500 µg/day topical swallowed budesonide for 50 weeks, after two weeks of induction treatment with 2000 µg/day of the same agent, was histologically effective in 50% of patients with EoE without any serious side effects. However, in that study, only two-thirds of patients achieved clinical response, and the authors commented that the maintenance dose of swallowed budesonide used (500 µg/day) might have been low. Therefore, in our patients, we lowered the dose of swallowed budesonide in a step-down fashion (25-50% of the previous dose) every three months according to clinical response. The swallowed budesonide dose was lowered to and maintained at 500 µg/day in four of our patients who showed complete clinical response during the follow-up period.

We followed our patients at three-month intervals unless the symptoms worsened. We monitored blood pressure and growth at every visit and referred all of our patients to the pediatric nutrition and metabolism, pediatric endocrinology and ophthalmology departments once a year for treatment-re-

lated side effects. No significant side effect was observed in our patients during the mean follow-up period of 13 months.

To date, few evidence exists about the natural history of EoE in children (11,12) and adults (25). The longest follow-up (14 years) with the greatest number of children (n=562) was done by Spergel et al. (12), who showed that only 1.95% of children with EoE developed clinical remission. There is no remission reported in adult studies with EoE (13,25). Also, in the study by Straumann et al. (24), 64.3% of adult patients with EoE who received placebo in the maintenance period after two weeks of induction treatment with 2000 µg/day of swallowed budesonide relapsed in three months. We achieved complete clinical response in all but one patient under elimination diet and/or corticosteroid treatment. Our study is a retrospective observational study; therefore, a repeat upper GI endoscopy and histological examination was not done if the patients showed complete clinical response within three months of the topical swallowed budesonide treatment except in one (Patient 3). Thus, we cannot comment on the histologic response. Since the longest follow-up in our report is 24 months, we cannot comment on clinical remission. However, only one of our patients (Patient 7) gave up a specific food elimination diet in the last six months and has remained asymptomatic until now.

In conclusion, EoE is a rare GI allergic disorder frequently comorbid with allergic respiratory diseases and with different manifestations and response profiles to treatment modalities. Since it is a chronic allergic disease with a very rare remission, management of these patients requires a teamwork consisting of allergists, gastroenterologists, pathologists, dieticians, and psychiatrists.

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