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Histopathologic findings of eosinophilic esophagitis in childhood

Çocukluk çağı eozinofilik özofajitlerinde histopatolojik bulgular

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Background and Aims: *Eosinophilic esophagitis, a rare allergic disease of the esophagus, was recently recognized as a distinct entity in children. Esophageal eosinophilia is the main histopathologic finding for its diagnosis, though it may be seen in various types of esophagitis. We, therefore, set out to evaluate the discriminatory value of currently available histologic criteria in the diagnosis of eosinophilic esophagitis in children.* ***Materials and methods:*** *We retrospectively evaluated the esophageal biopsies of 145 children, admitted to Ankara University Medical School hospital, who suffered from gastrointestinal symptoms, between 2007 and 2011, and retrieved 7 cases of clinically confirmed eosinophilic esophagitis. The presence of papillary elongation, dilatation of intercellular spaces and basal cell hyperplasia was noted together with the number of intraepithelial eosinophils, neutrophils, and lymphocytes per high-power field. Presence of necrosis/erosions, subepithelial inflammation and fibrosis, vascular congestion, and intestinal metaplasia was also recorded. Patients' medical records to retrieve data regarding demographic information, clinical presentation, laboratory data, endoscopic findings and the response to treatment received before upper gastrointestinal endoscopy.* ***Results:*** *The age of the patients ranged from 6-17 years with a mean age of 10.57±3.42 years. There were 3 boys and 4 girls. Endoscopic abnormalities such as white exudates and furrowing were found in three patients while four had normal endoscopy. Basal cell hyperplasia was found in three cases while papiller elongation was observed in 6 cases, three of which were mild and three were severe. Dilated intercellular spaces was observed in four cases, two of which were mild and two were severe. Eosinophilic microabscesses were observed in all cases. Median eosinophil count was 25 (min:12; max:78), while median lymphocyte count was 9 (min:2; max:33) within the squamous epithelium. No intraepithelial neutrophils were present.* ***Conclusion:*** *Histopathologic parameters such as epithelial eosinophilia (>15/hpf), eosinophilic microabscesses and superficial crowding of eosinophils seem to be the main diagnostic criteria for eosinophilic esophagitis in childhood in the correct clinical context. Basal cell hyperplasia, papillary elongation and dilatation of intercellular spaces seem to be less discriminatory for the diagnosis of eosinophilic esophagitis as they represent reactive changes to injury.*

Key words: *Eosinophilic esophagitis, histopathologic criteria, eosinophil counts*

Giriş ve Amaç: *Eozinofilik özofajit çocuklarda yeni tanımlanmış, özofagusun allerjik hastalığıdır. Diğer özofajit tiplerinde de izlenmekle birlikte özofageal eozinofili, eozinofilik özofajit tanısında temel histopatolojik bulgudur. Çalışmamızda çocuk yaş gurubunda eozinofilik özofajit tanısında histopatolojik kriterlerin tanımlayıcılığı değerlendirilmiştir.* ***Gereç ve Yöntem:*** *Çalışmamızda 2007-2011 yılları arasında Ankara Üniversitesi Tıp Fakültesi hastanesine gastrointestinal sistem şikayetleri ile başvuran 145 çocuk olgunun özofageal biyopsi materyalleri retrospektif olarak değerlendirilmiş ve klinik konfirmasyonu da sağlanan 7 eozinofilik özofajit olgusu çalışmaya dahil edilmiştir. Histopatolojik olarak papiller elongasyon, bazal hücre hiperplazisi ve dilate intersellüler boşluklar, büyük büyütme alanında saptanan intraepitelyal eozinofil, nötrofil ve lenfosit sayıları ile birlikte değerlendirilmiştir. Nekroz/erozyon varlığı, subepitelyal fibrozis ve inflamasyon bulguları da ayrıca değerlendirilmiştir. Hastaların demografik verileri, başvuru şikayetleri, endoskopi öncesi tedavi alıp almadıkları ve endoskopik bulguları hasta kayıtlarından edinilmiştir.* ***Bulgular:*** *Hastaların yaş ortalaması 10.57±3.42 (6-17 yaş) olarak saptanmıştır. Hastaların 3'ü erkek, 4'ü kız olup, olguların sadece 3'ünde özofagusta oluk şeklinde çizgilenme ve beyaz exudasyon olmak üzere anormal endoskopik bulgular saptanmıştır. Üç olguda bazal hücre hiperplazisi saptanırken, 3 olguda hafif, 3 olguda ise şiddetli olmak üzere toplam 6 olguda papiller elongasyon izlenmiştir. Ayrıca ikisi hafif ve ikisi şiddetli olmak üzere toplam 4 olguda dilate intersellüler boşluklar saptanmıştır. Olguların tümünde eozinofilik mikroabseler görülmüş ve ortanca eozinofil değeri 25 (min:12; max:78), ortanca lenfosit değeri ise 9 (min:2; max:33) olarak bulunmuştur. İntraepitelyal nötrofil görülmemiştir.* ***Sonuç:*** *Çocukluk çağında eozinofilik özofajit tanısına epitelyal eozinofili (>15 /hpf), eozinofilik mikroabseler ve yüzeyel eozinofilik dansite artışı gibi major histopatolojik parametrelerin klinik bulgularla birlikte değerlendirilmesiyle ulaşılabilir, papiller elongasyon, bazal hücre hiperplazisi ve dilate intersellüler boşluklar gibi minör histopathologic parametrelerin yol göstericiliği sınırlıdır.*

Anahtar kelimeler: *Eozinofilik özofajit, histopatolojik kriterler, eozinofil sayısı*

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by dense tissue eosinophilia (1). In EoE, biopsies show marked eosinophilic infiltrates at different levels of the esophagus. However, the presence of an increased number of eosinophils in the esophageal squamous epithelium is a nonspecific finding that may be seen in several disorders, including reflux esophagitis (RO), infections, drugs and Crohn's disease (2, 3). In order to distinguish EoE from other causes of mucosal eosinophilia, major and minor histologic criteria for the diagnosis of EoE have been described (4). Major features include epithelial eosinophilia of more than 15 eosinophils/high power field (hpf), and "microabscesses" described as clustering of 4 or more eosinophils and superficial layering of eosinophils. Minor criteria include basal cell hyperplasia (BCH), papiller elongation (PE), spongiosis (intercellular edema) which is currently known as dilated intercellular spaces (DIS), and inflammatory cell infiltration (4, 5). Both major and minor criteria, though helpful, are not pathognomonic for EoE as they may be seen in various types of esophagitis (2).

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We, therefore, decided to evaluate the discriminatory value of the currently available histologic criteria in the diagnosis of EoE in children.

MATERIALS AND METHODS

We retrospectively evaluated the esophageal biopsies of 145 children who underwent upper gastrointestinal endoscopy for various gastrointestinal symptoms in Ankara University Medical School hospital between 2007 and 2011, and retrieved 7 cases of clinically confirmed EoE.

Esophageal biopsies were taken from the middle and distal esophagus using standard biopsy forceps and were oriented with the luminal side upwards, embedded in paraffin and cut in 4 micrometer-thick sections and stained with hematoxylin and eosin (H&E). Histological assessment was performed by two pathologists together in a blinded manner, and the presence of PE (>50% of epithelial thickness) (Figure 1), DIS (Figure 2), and BCH (Figure 3) was noted in terms of severity graded as mild, moderate and marked, together with the number of intraepithelial eosinophils (Figure 4), neutrophils

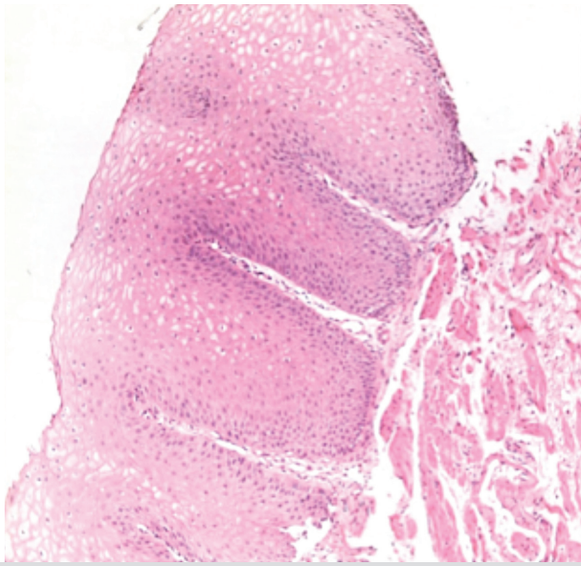

Figure 1. Papillary elongation >75% of epithelial thickness (H&E; X200).

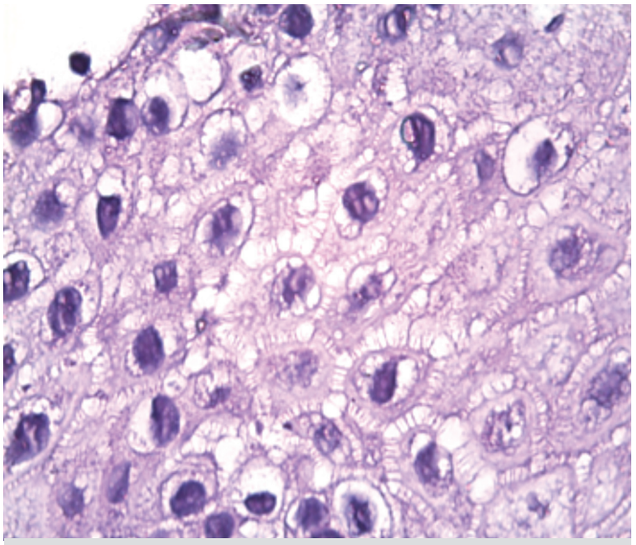

Figure 3. Dilated intercellular spaces between squamous cells in the form of bubbles and ladders (H&E; X400).

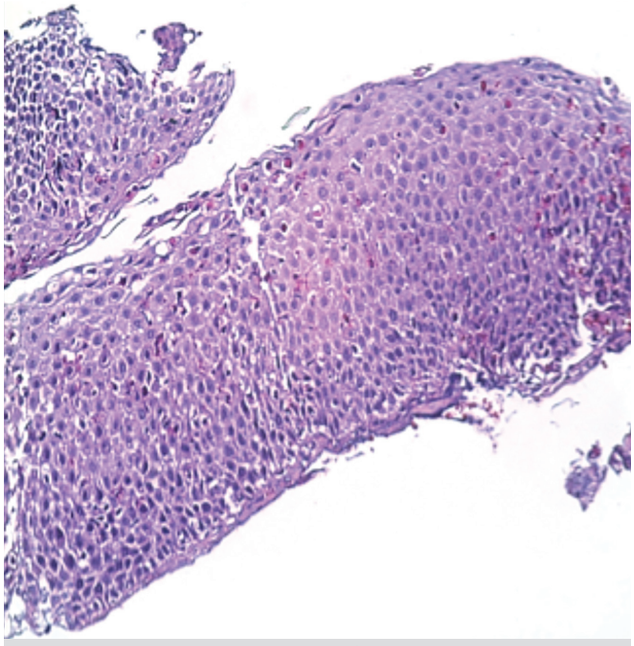

Figure 2. Basal cell hyperplasia >50% of the epithelial thickness (H&E; X200).

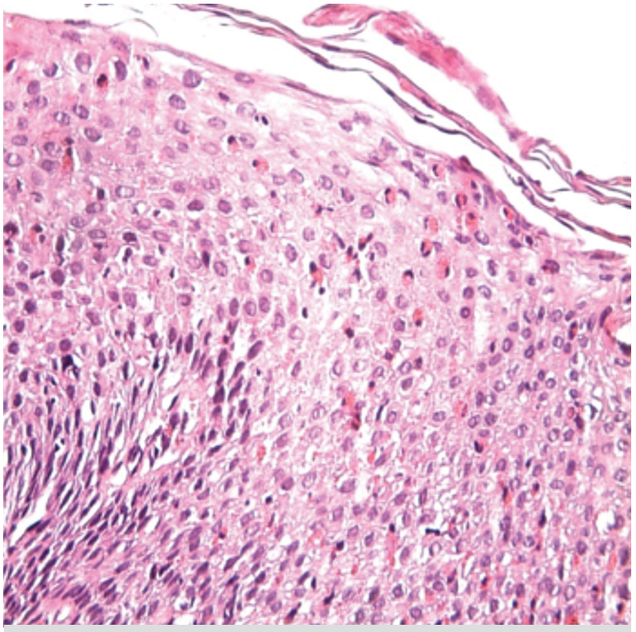

Figure 4. Marked intraepithelial eosinophilia and eosinophilic microabscesses (H&E; X200).

and lymphocytes (Figure 5) per hpf. Presence of necrosis/erosions, subepithelial inflammation and fibrosis, vascular congestion, and intestinal metaplasia was also recorded. When lesions were not homogenously distributed in a given sample, the area with the most severe change was evaluated. We analyzed the patients' medical records for data regarding demographic information, clinical presentation, laboratory data, endoscopic findings and the response to treatment given before upper gastrointestinal endoscopy.

RESULTS

Among 145 children who underwent upper gastrointestinal endoscopy for various gasrointestinal complaints, there were 7 cases consistent with a diagnosis of EoE. The age of the patients ranged from 6-17 years. There were 3 boys and 4 girls with a mean age of 10.57±3.42 years. Four patients were diagnosed as GERD refractory to adequate proton pump inhibitor (PPI) therapy before upper GI endoscopy. Among the 7 cases, 3 had GERD – like symptoms, 1 had abdominal pain, 1 had dysphagia, 2 of the patients were consultation cases with no clinical information. A total of 3 patients had concomitant allergic disease, which consisted of asthma in 1, and food allergy in 2 patients. Distribution of demographic features and clinical information are summarized in Table 1.

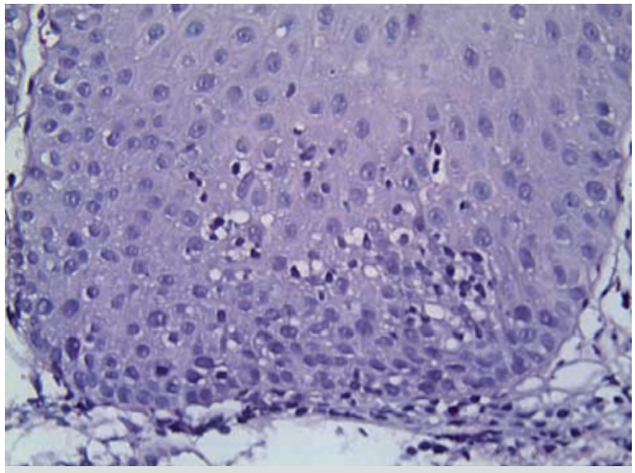

Figure 5. Lymphocytic infiltration in the squamous epithelium (H&E; X200).

In 3 patients with endoscopic abnormalities, 2 had white exudates and 1 had furrowing, while 4 cases presented with normal endoscopy.

Subepithelial inflammation was seen only in 1 case, whereas submucosal fibrosis was absent. BCH was found in 3 cases and PE in 6 cases, 3 of which were mild and 3 were severe. DIS was observed in 4 cases, 2 of which were mild and 2 severe. The distribution of endoscopic and histologic findings are summarized in Table 2.

Eosinophilic microabscesses were found in all cases with a eosinophil count of 25 (min:12; max:78). Four of our patients had >15/hpf intraepithelial eosinophils in their esophageal biopsies while the remaining three had 12 /hpf intraepithelial eosinophils. The mean lymphocyte count was 9 (min:2; max:33) while no neutrophils were determined in any of the cases.

DISCUSSION

There are very few studies on EoE in children, including a few case series from Turkey. Here, we described the demographic, endoscopic and histopathologic features of 7 children with EoE.

The exact etiopathogenesis of EoE is not well understood (2, 6, 7), though a history of atopy is commonly present in patients with EoE. 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's ring, and friability described as "crepe paper" mucosa, though not pathognomonic, are endoscopic signs of EoE (1). However, Pot-

Tablo 1. Demographic and clinical characteristics of cases

Number	Gender	Age (years)	Symptoms	Associated allergic disease	Serum specific IgE	Serum total IgE level (Iu/mL)	Peripheral eosinophil percentage (%)
1	M	17	Abdominal pain	Anaphylaxis (cow's milk)	Positive (Cow's milk)	92.7	6.1
2	M	6	Dysphagia	Asthma	Egg	197	10.5
3	F	13	GERD-like symptoms	None	Negative	NA	6.4
4*	F	10	NA	NA	NA	NA	NA
5*	M	10	NA	NA	NA	NA	NA
6	F	8	GERD-like symptoms	Asthma, allergic rhinitis	NA	138	9.3
7	F	10	GERD- like symptoms	None	Negative	8.9	3.2

NA: Not available, GERD-like symptoms: Vomiting, regurgitation and/or heartburn

*Consultation cases. There is no clinical information

Tablo 2. Endoscopic and histological findings of cases

Number	Endoscopic Findings		Histopathologic Findings					
	Linear furrows	White exudates	Peak eosinophil counts/hpf	Eosinophil clusters (micro-abscess)	Superficial eosinophilic density	PE	BCH	DIS
1	+	-	78	+	+	+	+	-
2	-	-	64	+	+	+	+	+
3	-	-	25	+	+	+	+	+
4	-	-	12	+	+	+	-	+
5	-	+	12	+	+	+	-	-
6	+	-	12	+	+	+	-	+
7	-	-	32	+	+	-	-	-

BCH: Basal cell hyperplasia, PE: Papillar elongation, DIS: Dilated intercellular spaces, NA: Not available, +: Observed, -: Not observed.

ter et al. (8) commented that when a patient had both esophageal narrowing and trachealization, a 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 (9, 10). In our series, 42.8% patients had abnormal endoscopic findings including white exudates and furrowing while the rest had normal endoscopy.

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 a threshold of >15 eosinophils in one high power field 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, gastroesophageal reflux disesase. In that review, epithelial eosinophilia (>15/hpf), eosinophilic microabscesses and superficial eosinophilic density are described as major, while PE, BCH, intercellular edema, and an increase in inflammatory cells were introduced as minor histopathologic features (4).

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 the diagnosis of EoE to 100% (11). In our EoE cases, a minimum of 2 and a maximum of 3 esophageal biopsies had been taken.

While all our cases presented with all major histologic features, minor histologic features were observed with varying incidences. This is in accordance with the current literature (1, 4, 7) which suggests that the minor criteria such as BCH, PE and DIS represent reactive changes of the squamous epithelium to injury, and thus, are nonspecific.

In conclusion, multiple biopsies and good orientation are critical for correct interpretation of features such as BCH, and PE while inflammatory cells, and in particular eosinophils, should be counted in areas where they are most numerous. Furthermore, presence of, eosinophilic "microabscesses" in the superficial squamous epithelium should be searched as they are present in almost all cases of EoE. Particularly in cases where the histopathology is less discriminatory, the diagnosis will rely upon a good clinicopathologic correlation, hence, the awareness of the physician and pathologist of EoE is mandatory for a correct diagnosis in children.

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