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ORIGINAL ARTICLE

Distribution of CD15+ and CD31+ Cells in the Oesophageal Mucosa of Children With Eosinophilic Oesophagitis Across Different Age and Sex Groups

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Abstract

Background/Aim: Eosinophilic oesophagitis (EoE) is a chronic immune-mediated inflammatory disease of the oesophagus with a multifactorial nature. The prognosis and effectiveness of therapy for EoE largely depend on a detailed study of its pathogenetic mechanisms. To clarify the severity of the inflammatory process, along with routine histological methods, a comprehensive immunohistochemical examination of the oesophageal mucosa was performed. To verify the intensity of tissue alterations, the marker CD15 was used and to assess the state of the vascular bed and the degree of vascularisation, the endothelial marker CD31 was employed. The aim of this research was to determine the morphometric features of the inflammatory process and tissue vascularisation in EoE in children of different age and sex groups.

Methods: A retrospective study included 94 children with EoE (ICD-10: K20), stratified into three age subgroups: Subgroup A (3–7 years), Subgroup B (8–12 years) and Subgroup C (13–18 years). The study utilised clinical data and morphological methods (general histology, histochemical reactions – Masson's trichrome and periodic acid–Schiff (PAS) and immunohistochemical analysis for CD15 and CD31) for examining biopsy material from the oesophageal mucosa.

Results: Distinct age- and sex-dependent patterns were identified. In male patients, peak CD15+ cell density was recorded in Subgroup A, demonstrating a significant 1.57-fold decrease toward the adolescent group ($p < 0.05$). Conversely, female patients demonstrated the lowest CD15+ density in Subgroup A, with a significant 1.89-fold increase in Subgroup C ($p < 0.05$), where female CD15+ density exceeded males by 1.94 times ($p < 0.05$). All assessed microvascular parameters progressively increased from Subgroup A to C in both sexes ($p < 0.05$). When comparing by sex in the older age cohort, the microvascular density in girls significantly exceeded that in boys by 1.18 times ($p < 0.05$).

Conclusion: EoE in children is characterised by distinct age- and sex-dependent inflammatory and structural changes in the oesophageal mucosa. Immunohistochemical analysis revealed prominent epithelial CD15 expression reflecting the intensity of cellular alteration and CD31+ endothelial reactivity reflecting a microvascular response during the development of the disease. The results underscore the importance of comprehensive diagnostics, including detailed morphological, histological and immunohistochemical evaluation of the mucosa, which may provide valuable insights for improving diagnostic strategies and monitoring disease progression.

Key words: Oesophagus; Eosinophilic oesophagitis; Lewis x antigen; CD15; Platelet endothelial cell adhesion molecule-1; CD31; Child.

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Introduction

Eosinophilic esophagitis (EoE) is a multifactorial chronic inflammatory disease of the oesophagus with a pronounced immune component.[1, 2] The pathogenetic basis of this disease is a combination of genetic disorders with the activation of immune processes, primarily following the Th2-response pathway and initiated by cytokines such as interleukins (IL) 4, 5 and 13.[1-4] As is known, these cytokines induce the expression of specific chemokines, particularly eotaxin-3 (CCL26).[5] By binding to eosinophil membrane receptors (CCR3), CCL26 acts as a potent chemoattractant, stimulating their migration into oesophageal tissue with subsequent degranulation.[5, 6] The release of toxic proteins and inflammatory mediators leads to prolonged epithelial damage, impairment of its barrier function and simultaneous stimulation of fibroblast proliferation, which in the long term results in fibrotic remodelling of the oesophagus.[7]

Over the past three decades, the prevalence of this disease has increased more than eightfold, placing it among the top three most common inflammatory oesophageal diseases and establishing it as a significant new epidemiological problem on a global scale.[8] EoE most frequently affects males, particularly male children and adolescents, which undoubtedly underscores the importance of timely diagnosis and the development of individualised treatment approaches.[9] The clinical presentation of EoE varies depending on age. Patients often develop compensatory eating strategies to avoid symptoms (eg prolonged chewing of food, excessive drinking of water, avoidance of specific foods such as meat or bread).[10] In infants and young children, the disease more commonly manifests as feeding difficulties, vomiting, irritability, or failure to thrive, whereas in adolescents and adults, the main complaints are dysphagia, decreased appetite, chest and/or abdominal pain and other non-specific symptoms.[11, 12]

The prognosis and success of therapy for EoE, as with any other pathology, largely depends on a detailed study of its pathogenetic mechanisms. This approach is particularly relevant in paediatric practice, as children of different age groups exhibit unique clinical and pathogenetic features, the timely diagnosis of which is critical for preventing the development of complications.[11]

The generally accepted diagnostic standard for EoE is esophagogastroduodenoscopy with mandatory collection of multiple biopsies (recommended at least 6 samples) from the proximal and distal parts of the oesophagus, followed by histological examination.[13] However, despite the high accuracy of this methodological approach, standard staining and evaluation methods for microscopic slides have a number of limitations, preventing a detailed study of the full molecular and cellular picture.[14]

Complementing its primary Th2-associated nature, increasing evidence points to the complex involvement of various cellular and tissue alterations in mucosal damage and subsequent remodelling in EoE. Specifically, the expression of the cell adhesion molecule CD15 serves as a prominent indicator of epithelial cell stress, activation and reactive changes during active tissue injury, while microvascular alterations (evaluated via CD31) are key to oesophageal remodelling during the chronic course of the disease. Despite existing data, the specific relationship between epithelial cell reactivity and vascularisation processes across different paediatric age and sex groups remains insufficiently explored.

Therefore, investigating the density of immunopositive cells (CD15+) and the vascular response (CD31+) as components of the inflammatory-reparative process in patients of different sexes and age groups may provide insights into the divergent clinical phenotypes and contribute to a better understanding of disease progression.

Aim of the study was to evaluate the density of CD15-immunopositive cells and CD31-mediated vascular response in the oesophageal mucosa of children with EoE with specific emphasis on defining age- and sex-specific pathomorphological profiles.

Methods

Based on anamnestic and clinical-morphological data, a single group of patients was formed (n = 94; age 3–18 years). The cohort included 57 males

and 37 females, with a mean age of 12.5 ± 3.2 years. In accordance with the age classification of children recommended by the World Health Organisation, the patient group was divided into three subgroups (Table 1):

– Subgroup A – early childhood (3–7 years, n = 11);
– Subgroup B – middle childhood (8–12 years, n = 22);
– Subgroup C – adolescents (13–18 years, n = 61).

Table 1: Age stratification of children

Subgroup	Male (n)	Female (n)
A – early childhood (3 – 7 years)	6	5
B – middle childhood (8 – 12 years)	13	9
C – adolescents (13 – 18 years)	38	23
Total	57	37
	94	

The study was performed using archived paraffin biopsy samples of the oesophageal mucosa obtained during oesophagogastroduodenoscopy. Inclusion criteria were: Clinical diagnosis of EoE (ICD-10: K20 / ICD-11: KB81.0); Patient from 3 to 18 years of age. Exclusion criteria were: Presence of comorbid gastrointestinal diseases that could affect the morphological parameters of the oesophagus (peptic ulcer disease, gastroesophageal reflux disease, specific infections); Endocrine and autoimmune diseases, HIV infection, viral hepatitis B and C, diabetes mellitus and other systemic diseases; Signs of systemic inflammatory or oncological diseases and use of medications (eg systemic steroids, immunosuppressants, or antibiotics); Injuries to the oesophagus related to trauma or medical procedures.

The diagnosis of EoE was confirmed based on integrated clinical, endoscopic and histological findings. Within the study group, 74 % of patients (n = 70) had a history of allergic diseases (atopic dermatitis, bronchial asthma, allergic rhinitis) and 53 % (n = 50) reported food intolerance or a family history of atopy.

Morphological examination

Fragments of oesophageal mucosal biopsies were fixed in 10 % buffered formalin, dehydrated in increasing concentrations of alcohol, cleared in xylene and embedded in paraffin. From the resulting paraffin blocks, sections 3 µm thick were prepared and placed on adhesive glass slides. Sections were deparaffinised, rehydrated and stained with haematoxylin and eosin (H&E) according to a standard protocol.

To assess fibrosis, one slide from each batch was additionally stained with Masson's trichrome using a modified protocol (employing Weigert's haematoxylin, acid fuchsin, phosphomolybdic acid and aniline blue). The degree of fibrosis was assessed semi-quantitatively using a scoring system, considering the area and optical density of fibre staining in relative units (ru): "0" – absent; "1" – mild (0–0.3 ru; < 25 % area); "2" – moderate (0.3–0.6 ru; 25–50 %); "3" – pronounced (0.6–0.9 ru; 50–75 %); "4" – severe (> 0.9 ru; > 75 %).

The vascularisation of the oesophageal mucosa was quantitatively assessed using the following parameters: microvessel density (MVD), defined as the number of CD31+ vessels per 1 mm^2; relative vascular area (RVA), representing the percentage of the *lamina propria* occupied by the vascular bed; mean vessel area (MVA), indicating the average cross-sectional area of a single blood vessel (μm^2). Morphometric analysis was performed in 10 randomly selected fields of view per section at ×400 magnification, followed by calculation of mean values for each biopsy sample.

Immunohistochemical study

Immunohistochemical (IHC) study was performed on an automated Ventana BenchMark IHC system (*Leica Biosystems*, Germany) according to the standard protocol and manufacturer's recommendations. The following primary monoclonal antibodies were used: VENTANA anti-CD15 (MMA) Monoclonal Primary Antibody (11 µg/mL; *Roche Diagnostics*) and FLEX Ready-to-Use Monoclonal Mouse Anti-Human CD31 Endothelial Cells (JC70A; *Dako, Agilent*).

Assessment of marker expression intensity and quantitative analysis of immunopositive cells were performed using an image analysis system after scanning the sections on a Leica Aperio AT2 scanner. Quantification was done both parametrically (calculating the number of positive cells per 1 mm^2) and in absolute values using QuPath V.0.5.1 digital pathology software. This analysis was performed independently by two researchers blinded to the clinical data, assessing the overall cell density within both the epithelial layer and lamina propria in five representative mucosal regions for each sample. Inter-observer

discrepancies exceeding 10 % were resolved by joint re-evaluation to reach a consensus.

Statistical analysis

Statistical analysis of the sample was performed using STATISTICA 13.5.0.17 software (*TIBCO Software* inc). The Shapiro-Wilk test was used to assess the normality of the data distribution. For comparisons between study groups with non-normal distributions, the Kruskal-Wallis test followed by Dunn's post-hoc test with Bonferroni correction for multiple comparisons was applied. Pairwise comparisons were performed using the Mann-Whitney U test with the appropriate adjustment of the significance level. A p-value ≤ 0.05 was considered statistically significant.

Results

Endoscopic (macroscopic) findings

Endoscopic examination revealed that active inflammatory changes were present in 48 % (n = 45) of the total cohort. The most frequent inflammatory signs, including mucosal oedema (43 %, n = 40), longitudinal furrows (36 %, n = 34) and whitish exudates (31 %, n = 29), predominated in Subgroups A and B (Table 2), showing a non-significant downward trend toward the adolescent subgroup (p > 0.05).In contrast, signs of structural remodelling, including eosinophilic rings (36 %, n = 34) and strictures (32 %, n = 30), were significantly more prevalent in Subgroup C compared to the younger subgroups (p < 0.05).

No statistically significant differences in the frequency of endoscopic signs between boys and girls were found (p > 0.05). Notably, in 10 % (n = 9) of patients, the oesophageal mucosa appeared macroscopically normal despite histological confirmation of EoE.

Morphological findings

Microscopic assessment of the inflammatory reaction in the oesophageal mucosa revealed several characteristic changes, the severity of which varied depending on the patient's sex and age. Pronounced epithelial eosinophilic infiltration exceeding the diagnostic threshold (> 15 eosinophils per high-power field, HPF) was observed in all patients (n = 94). Specific histological alterations of the oesophageal epithelium including eosinophilic microabscesses, dilated intercellular spaces, surface epithelial desquamation and basal cell hyperplasia were present across all age groups without significant variation (Table 2, p > 0.05).

Table 2: Comparative analysis of clinical and morphological features in children with eosinophilic oesophagitis (EoE) by age and sex

Category / Parameters	Subgroup A		Subgroup B		Subgroup C	
	Boys (n = 6)	Girls (n = 5)	Boys (n = 13)	Girls (n = 9)	Boys (n = 38)	Girls (n = 23)
Inflammatory pattern, n (%)						
Oedema	4 (67 %)	2 (40 %)	8 (62 %)	5 (56 %)	14 (37 %)	7 (30 %)
Exudate	2 (33 %)	1 (20 %)	6 (46 %)	3 (33 %)	13 (34 %)	4 (17 %)
Furrows	3 (50 %)	2 (40 %)	7 (54 %)	5 (56 %)	12 (32 %)	5 (22 %)
Peak eosinophil count, cells/HPF	38 ± 12	45 ± 15	42 ± 11	61 ± 25	35 ± 14	39 ± 16
Eosinophilic microabscesses	4 (67 %)	4 (80 %)	10 (77 %)	7 (78 %)	18 (47 %)	14 (61 %)
Dilated intercellular spaces	5 (83 %)	4 (80 %)	11 (84 %)	8 (88 %)	27 (71 %)	15 (65 %)
Surface desquamation	5 (83 %)	4 (80 %)	8 (62 %)	7 (78 %)	15 (39 %)	11 (48 %)
Mucin production (PAS+)	4 (67 %)	3 (60 %)	7 (54 %)	7 (78 %)	16 (42 %)	13 (57 %)

Remodelling pattern, n (%)						
Rings	1 (17 %)	0 (0 %)	2 (15 %)	1 (11 %)	20 (52 %) *	10 (43 %) *
Strictures	0 (0 %)	1 (20 %)	1 (8 %)	2 (22 %)	17 (45 %) *	9 (39 %) *
Basal cell hyperplasia	4 (67 %)	3 (60 %)	9 (69 %)	6 (67 %)	30 (79 %)	18 (78 %)
Fibrosis (Masson) frequency **	2 (33 %)	2 (40 %)	9 (69 %)	7 (78 %)	32 (84 %) *	20 (87 %) *
Severity, M ± SD	2.2 ± 0.3	2.0 ± 0.4	2.7 ± 0.4	2.4 ± 0.5	3.1 ± 0.5 * #	2.6 ± 0.4 *

*Data are presented as n (%) or mean (M) ± standard deviation (SD); * – p < 0.05 compared to Subgroup A. ** – assessed in the lamina propria using Masson's trichrome stain, percentages represent patients with moderate to severe fibrosis (grade ≥ 1). # – p < 0.05 compared to female patients within the same subgroup; PAS: periodic acid–Schiff;*

Evaluation of the secretory activity revealed the excessive accumulation of PAS-positive material (mucin) in the epithelial layer across all subgroups (Figure 1). A higher frequency and qualitative intensity of mucin production were observed in younger children (Subgroups A and B) and in female patients, although these differences did not reach statistical significance (Table 2, p > 0.05). Subepithelial remodelling processes of the mucosa, identified by Masson's trichrome staining, demonstrated a significant correlation with patient age: their frequency and severity progressively increased toward the older subgroup compared to younger patients (p < 0.05).

In the younger subgroup, fibrosis was characterised by a predominance of thin, chaotically arranged collagen fibres. In contrast, the middle and older subgroups exhibited a more mature structure with dense collagen bundles and signs of perivascular sclerosis (Figure 1). Notably, when comparing the severity of fibrosis by sex, the manifestation was more pronounced in boys than in girls, especially in the adolescent group (Table 2, p < 0.05).

Immunohistochemical findings

The density of CD15-positive cells (a cell adhesion molecule, also known as Lewis x), demonstrated these markers in oesophageal squamous cells using immunoperoxidase techniques. Studies have shown that it is possible to label disaggregated oesophageal epithelial cells with CD15. In mucosa: CD15 staining is often used to identify immune

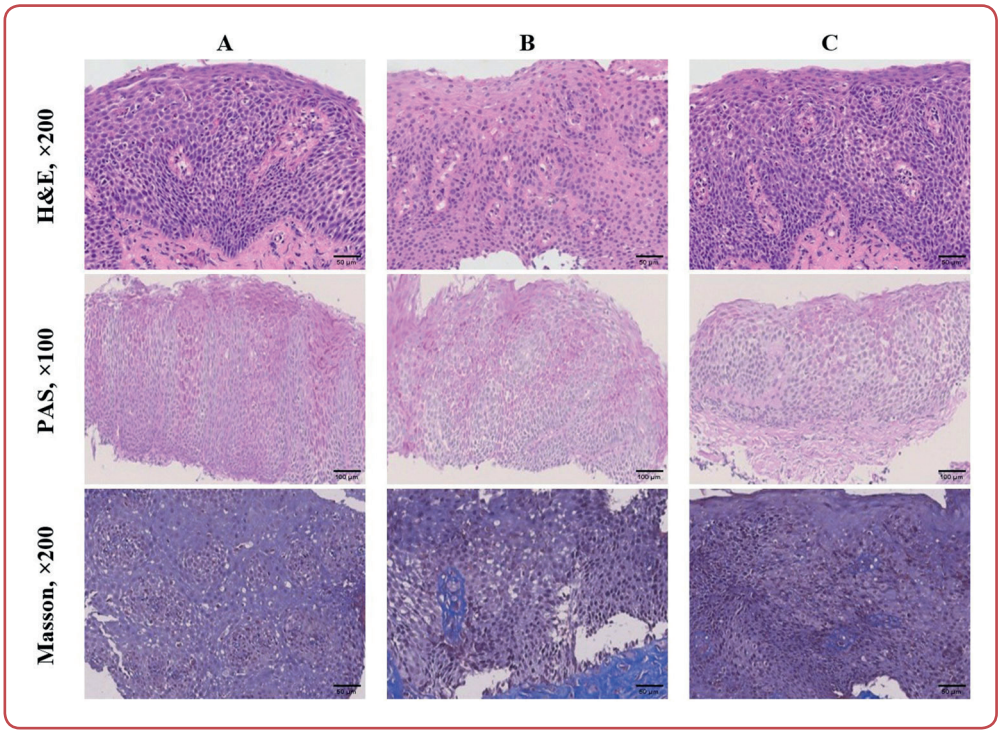

Figure 1: Histological (haematoxylin and eosin - H&E) and histochemical (periodic acid–Schiff - PAS) reaction, Masson's trichrome reaction) features of the oesophageal mucosa in eosinophilic oesophagitis (EoE)

cells of infiltration (myeloid cells and eosinophils; activated B and T cells), which is associated with inflammation and the grade of reactive changes or dysplasia.

In the oesophageal mucosa of male patients, the maximum values were recorded in Subgroup A and demonstrated a significant decrease by 1.57 times compared to the older subgroup ($p < 0.05$). In female patients, on the contrary, the minimum CD15+ cell density was observed in Subgroup A, with a significant 1.89-fold increase observed in the older age group (Table 3, $p < 0.05$). When comparing by sex in the older age cohort, the density of CD15+ cells in girls was significantly higher than that in boys by 1.94 times ($p < 0.05$).

CD15-immunopositive cells were verified not only as part of the inflammatory infiltrate but were also predominantly identified as clear membranous and cytoplasmic staining of the stratified squamous epithelium of the oesophagus (Figure 2 and 3).

Immunohistochemical staining for CD31 demonstrated prominent expression of the marker within the endothelial cells of the oesophageal mucosa (Figure 4 and 5). The study found that in male patients, each of the measured vascularisation indicators, including MVD, RVA and MVA in Subgroup C significantly exceeded those in Subgroup A by 1.55, 1.56 and 1.38 times, respectively ($p < 0.05$). Female patients demonstrated a similar trend, with Subgroup C exhibiting a 1.62-, 1.52- and 1.39-fold increase in MVD, RVA and MVA values compared to Subgroup A (Table 3, $p < 0.05$).

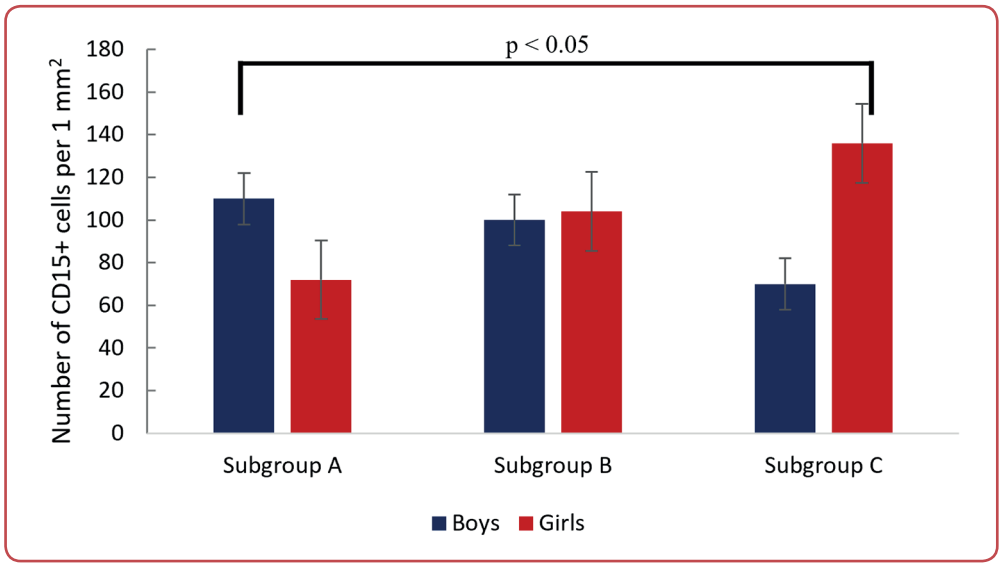

Figure 2: Density of CD15+ cells in the oesophageal mucosa according to patient age and sex
The x-axis represents study groups (age subgroups and patient sex); the y-axis represents numerical cell density (number of CD15+ immunopositive cells per 1 mm²);

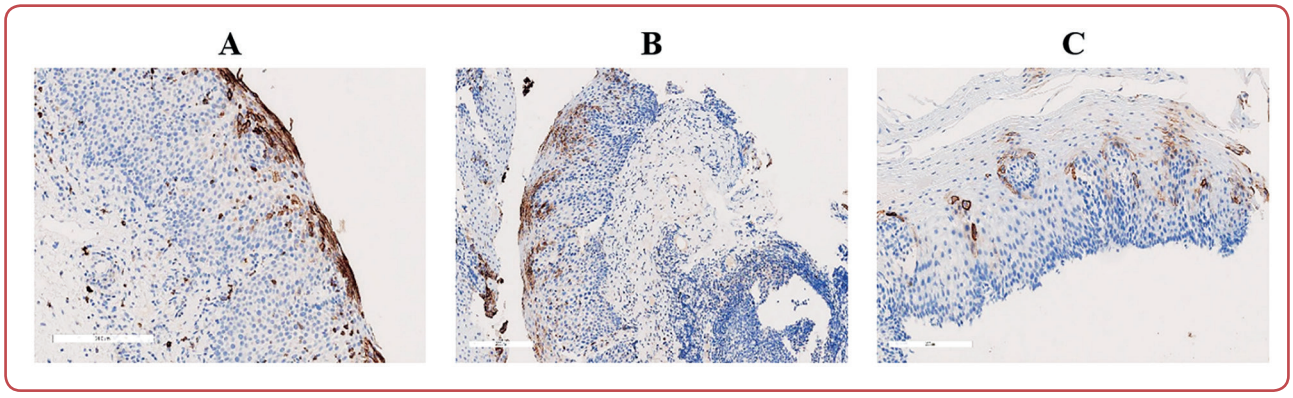

Figure 3: Immunohistochemical staining for CD15 in oesophageal mucosa, magnification ×200

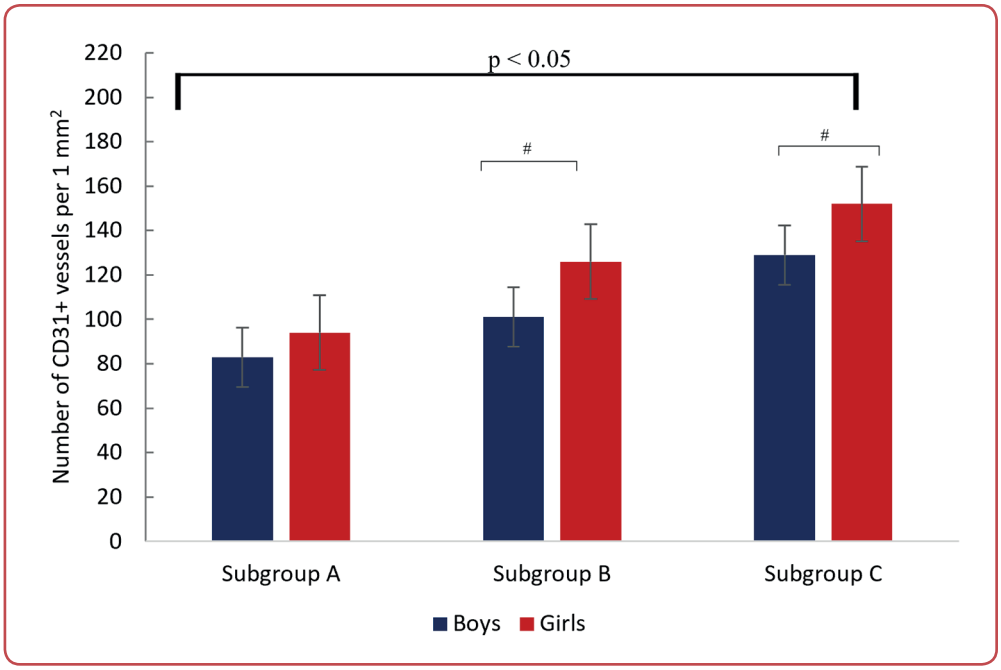

Figure 4: Microvessel density in the oesophageal mucosa according to patient age and sex
The x-axis represents patient study subgroups; the y-axis represents the numerical vessel density (number of vessels per 1 mm²) # – p < 0.05 compared to male patients within the same age group;

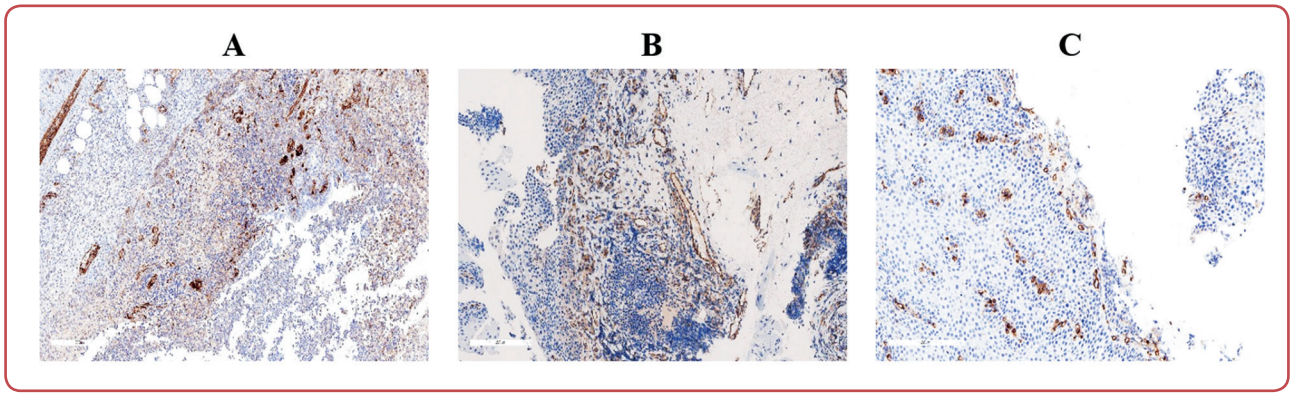

Figure 5: Immunohistochemical staining for CD31 in oesophageal mucosa, magnification ×200

In intergroup comparison by sex, statistically significant differences were verified in the middle and older age subgroups only for MVD: this indicator in girls was higher than the same parameter in boys by 1.25 and 1.18 times, respectively (Figure 4, $p < 0.05$).

Quantitative IHC analysis revealed statistically significant age-related differences in the distribution of inflammatory and vascularisation markers (Table 3).

Table 3: Quantitative immunohistochemical parameters of the oesophageal mucosa by age and sex

Category / Parameters	Subgroup A	Subgroup B	Subgroup C
CD15+ density, cells/mm²			
Boys	110 ± 18	100 ± 16	70 ±12 *
Girls	72 ± 12	104 ± 18	136 ± 22 * #
MVD (CD31+), vessels/mm²			
Boys	83 ± 17	101 ± 21	129 ±25 *
Girls	94 ± 20	126 ± 24 #	152 ± 28 * #

RVA, %			
Boys	6.6 ± 1.4	8.3 ± 1.6	10.3 ± 1.9 *
Girls	7.5 ± 1.5	9.6 ± 1.7	11.4 ± 2.1 *
MVA, μm²			
Boys	24.3 ± 2.8	28.1 ± 3.3	33.5 ± 3.9 *
Girls	25.8 ± 2.9	30.2 ± 3.5	35.9 ± 4.2 *

*Data are presented as mean (M) ± standard deviation (SD); * – $p < 0.05$ compared to Subgroup A; # – $p < 0.05$ compared to male patients within the same age group. MVD: microvessel density; RVA: relative vascular area; MVA: mean vessel area.*

Discussion

This study conducted an IHC assessment of the inflammatory infiltrate characteristics and reparative response in the oesophageal mucosa of children with EoE, revealing important pathomorphological features of the disease. The obtained results confirm that EoE is characterised by pronounced structural and functional alterations of the mucosa, involving both reactive remodelling of the epithelial layer and concurrent reorganisation of the microvascular bed.[2, 5, 15]

According to the study results, male patients in the older age subgroup demonstrated a lower density of CD15-positive cells, coupled with an increase in the severity of subepithelial fibrosis, vascularisation indicators and the frequency of strictures and eosinophilic rings. Collectively, these data may indicate pronounced age- and sex-specific patterns of tissue changes in EoE. This suggests that within the older age cohort of male patients, the morphological profile of the disease shifts from predominantly alterative tissue processes toward chronic structural remodelling of the organ wall, a finding supported by data from other authors.[7, 12] Female patients exhibit a different morphological profile: within the older age subgroup, maximum values are reached across all evaluated parameters, including the density of CD15-positive cells, tissue vascularisation indicators, the frequency of endoscopic remodelling patterns and subepithelial fibrosis, as well as its severity, suggesting the formation of a systemic tissue response.

In an intergroup comparison by sex, a significantly higher density of CD15-positive cells and MVD indicators was observed in adolescent girls, combined with a significantly lower severity of fibrosis compared to age-matched boys. This suggests a predominance of exudative-alterative tissue changes in adolescent female patients, whereas in male patients, the tissue profile shifts toward more severe fibrotic remodelling, which aligns with literature data indicating the existence of sex differences in the immune response.[12, 16]

The identified age and sex patterns allow for personalising approaches to disease diagnosis and monitoring. Furthermore, our obtained data underscore the importance of accurate differential diagnosis of EoE from other oesophageal diseases (eg reflux oesophagitis). Since these nosological forms require fundamentally different treatment approaches, the use of immunohistochemistry (markers such as CD15, CD31 and others) may potentially serve as complementary research tools that will help avoid diagnostic errors and optimise therapeutic strategies.

Considering certain limitations of this study (retrospective design using archival material, which does not allow for a full assessment of the dynamics of pathological changes over time; a relatively small sample size in some subgroups; the absence of molecular genetic methods), future research plans include prospective patient follow-up incorporating functional tests (eg assessment of epithelial barrier function) and the use of multiplex immunohistochemistry to analyse cell interactions. This will allow for a better understanding of sex differences and the development of biomarkers for early intervention. Thus, based on this study, it can be concluded that the results obtained expand the current understanding of mucosal structural remodelling in EoE, potentially contributing to a more individualised approach to patients.

Conclusion

EoE in children is characterised by distinct age- and sex-dependent inflammatory and structural changes in the oesophageal mucosa. Immunohistochemical analysis revealed prominent epithelial CD15 expression reflecting the intensity of cellular alteration and CD31+ endothelial reactivity reflecting a microvascular response during the development of the disease. The obtained results underscore the importance of comprehensive diagnostics, including detailed morphological, histological and immunohistochemical evaluation of the mucosa, which is of key significance for early detection of the disease and selection of an appropriate therapeutic strategy.

Ethics

The conduct of this study was approved by the Local Ethics Committee of the "Morozov Children's City Clinical Hospital" (Protocol No 7, dated 10 November 2024). All procedures were conducted in strict compliance with the ILAR guidelines for the care and use of laboratory animals, the "International recommendations for conducting biomedical research using animals" (EEC, Strasbourg, 1985) and the "European convention for the protection of vertebrate animals for experimental and other scientific purposes" (EEC, Strasbourg, 1986).

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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