

Standardisation of histologic reporting in eosinophilic oesophagitis: Expert recommendations

Carla Giordano^{1*}, Valentina Angerilli^{2*}, Marco Masci¹, Maria D'Armiento³, Paola Parente⁴, Emanuela Pilozzi⁵, Alessandro Vanoli^{6,7}, Salvatore Oliva⁸, Edoardo Vincenzo Savarino⁹, Matteo Fassan^{10,11*}, Luca Mastracci^{12,13*}

¹ Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy; ² Surgical Pathology Unit, ULSS2 Marca Trevigiana, Treviso, Italy; ³ Department of Public Health, School of Medicine, University "Federico II", Naples, Italy; ⁴ Unit of Pathology, IRCCS Casa Sollievo della Sofferenza Foundation, San Giovanni Rotondo, Italy; ⁵ Department of Clinical and Molecular Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy; ⁶ Department of Molecular Medicine, University of Pavia, Pavia, Italy; ⁷ Unit of Anatomic Pathology, IRCCS San Matteo Hospital Foundation, Pavia, Italy; ⁸ Pediatric Gastroenterology and Liver Unit, Maternal and Child Health Department, Sapienza University of Rome, Rome, Italy; ⁹ Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy; ¹⁰ Department of Medicine (DIMED), University of Padua, Padua, Italy; ¹¹ Veneto Institute of Oncology (IOV-IRCCS), Padua, Italy; ¹² Pathology Unit, Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy; ¹³ IRCCS San Martino Policlinic Hospital of Genoa, Genoa, Italy.

* All authors equally contributed to the manuscript.

Summary

Over the past decade, significant progress has been made in understanding eosinophilic oesophagitis (EoE), leading to the refinement of diagnostic criteria and the development of evidence-based management guidelines. Nevertheless, despite the central role of histology in both diagnosis and disease monitoring, significant variability remains in histopathological reporting across institutions and among pathologists. This study seeks to provide recommendations for standardised histological reporting in EoE. To this end, a multidisciplinary panel of gastroenterologists and pathologists convened to review current practices and address persistent challenges in histologic assessment. Through an extensive literature review and critical appraisal of existing scoring systems, the panel reached consensus on both essential and desirable histological features for routine reporting, including eosinophil counts, additional inflammatory parameters, and fibrostenotic changes.

Key words: Eosinophilic oesophagitis, follow-up, histopathology, standardisation, diagnosis

Introduction

Eosinophilic oesophagitis (EoE) is a chronic, relapsing, type 2 immune-mediated disorder characterised by eosinophil-predominant inflammation of the oesophageal mucosa¹. Over time, the disease progresses from an inflammatory to a fibrostenotic phenotype. The estimated incidence of this underdiagnosed condition currently ranges from approximately 1 to 20 cases per 100,000 person-years¹⁻⁴, with a prevalence of up to 20% in adults undergoing endoscopy for dysphagia or food impaction. A rising trend is observed in both pediatric and adult populations, reflecting not only growing clinical awareness but also a true increase in disease burden³.

Over the past three decades, significant advances in the understanding of EoE have led to the development and refinement of diagnostic criteria

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Correspondence

Carla Giordano

E-mail: carla.giordano@uniroma1.it

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ria and evidence-based management guidelines^{1-3,5-8}. Histologic examination of oesophageal biopsies remains the cornerstone of diagnosis and monitoring of disease activity during treatment. A definitive diagnosis requires both clinical symptoms of oesophageal dysfunction and the presence of ≥ 15 eosinophils per high-power field (eos/hpf) (hpf, standardized size of 0.3 mm^2) in ≥ 1 biopsy specimen, ruling out secondary causes of oesophageal eosinophilia. Additional histologic features, such as eosinophilic microabscesses, basal zone hyperplasia, dilated intercellular spaces, surface epithelial alterations, and lamina propria fibrosis, can further delineate disease activity and severity⁹ and have been recently integrated in a scoring system (i.e., Eosinophilic Oesophagitis Histologic Scoring System, EoEHSS)¹⁰. This validated score has demonstrated superior sensitivity to treatment effects compared to eosinophil counts alone¹¹.

To further enhance standardisation and support longitudinal disease management, the Index of Severity for Eosinophilic Oesophagitis (I-SEE) was recently introduced⁷, integrating clinical, endoscopic, and histological parameters. However, despite the central role of histology in both diagnosis and follow-up, there remains significant variability in histologic reporting across institutions and among pathologists. This inconsistency can hinder accurate diagnosis, assessment of treatment response, and comparability of findings between centres.

This study aims to establish recommendations for standardized histological reporting in EoE. To this end, an overview of relevant clinical and endoscopic features that may support histologic assessment will be provided. Elementary lesions allowing EoE histopathology diagnosis will be described, and recommendations for standardised histologic reporting in EoE will be presented.

Materials and methods

An expert panel consisting of two Italian gastroenterologists (S.O. and E. V.S.) and eight Italian gastrointestinal pathologists with experience in EoE (V.A., M.d.A., P.P., E.P., A.V., M.F., L.M., C.G.) convened for a one-day advisory board meeting on 30th June 2025. Before the meeting, a comprehensive literature review was conducted focusing on EoE histological features, existing scoring systems, and their clinical implications (search terms included: “oesophagitis”, “oesophageal biopsies”, “eosinophilic oesophagitis guidelines and recommendations”, and “oesophagitis scores”).

The panel reviewed current practices, discussed challenges in EoE histological reporting, evaluated the

strengths and limitations of existing scoring systems (particularly the EoEHSS and I-SEE), and developed recommendations for standardising histologic reports for EoE.

Ethical approval was not required for this consensus study, as it did not involve human participants or patient data.

Results

CLINICAL FEATURES

EoE has been reported throughout the lifespan, with a prevalence in males and peaks in early adulthood¹. The clinical manifestations of EoE are heterogeneous and may vary depending on the patient's age and sex¹², mechanisms of swallowing adaptation, disease behaviour and progression (i.e., stage of inflammation or fibrosis), and ongoing therapy^{12,13}. Feeding difficulties and failure to thrive are frequent in infants. Vomiting, poor appetite, retrosternal pain, and heartburn are common in children. Notably, at this age, symptoms may overlap with those of gastro-oesophageal reflux disease (GERD). Although they are distinct conditions, EoE and GERD can coexist and interact within the same patient. Specifically, GERD can increase the risk of developing EoE by altering the permeability of the oesophageal barrier¹⁴. The complex interplay between EoE and GERD is further highlighted by the observation that proton pump inhibitor (PPI) therapy can induce both clinical and histological remission in patients with EoE¹. In adults, the most common manifestations of EoE are dysphagia and food impaction. Interestingly, adult patients often neglect these symptoms, meaning that they may first encounter a physician in the emergency department due to oesophageal food impaction¹⁵.

ENDOSCOPIC FEATURES AND BIOPSY PROTOCOL

The endoscopic features of EoE are represented by signs of active inflammation (oedema, exudates, and longitudinal furrows) and fibrostenotic remodelling of the oesophagus (rings, strictures, narrowing, and crêpe-paper mucosa)⁷. To standardise the nomenclature and scoring of endoscopic findings, the EoE endoscopic reference score (EREFS) has been developed based on the following five major findings: oedema, rings, exudates, furrows, and strictures¹⁶.

Furthermore, because eosinophilic infiltration is often patchy, multiple biopsies are recommended to improve diagnostic accuracy, typically 6 from ≥ 2 oesophageal sites, combining targeted and random sampling⁵. To allow correlation between histologic findings and

endoscopic features, the biopsies must be submitted in separate containers for each anatomical site (i.e. proximal, middle, and distal oesophagus). In 5-32% of patients with EoE, the oesophageal mucosa may appear normal at endoscopy; thus, biopsies must be performed regardless of its endoscopic appearance^{17,18}.

HISTOPATHOLOGIC FEATURES

Eosinophil morphology

Eosinophils are granulocytic leucocytes measuring approximately 10-15 μm in diameter. They are characterised by a bilobed nucleus, often connected by a thin chromatin strand with deeply condensed basophilic chromatin that contrasts sharply with the surrounding cytoplasm. The cytoplasm is abundant and densely filled with large, uniform, eosinophilic granules that stain bright orangish red with haematoxylin and eosin (H&E). These granules measure approximately 0.5-1 μm in diameter and are highly refractile, often obscuring the nucleus when the cells are closely packed. The granules' strong eosinophilia is because they are composed of basic proteins such as major basic protein (MBP), which is a key component implicated in tissue damage during eosinophil-mediated diseases. The presence of intact granules indicates resting or non-activated eosinophils, whereas degranulation is recognised histologically by the presence of extracellular granules and disruption of granule integrity within the cytoplasm¹⁹.

Diagnostic criteria and accompanying morphologic alterations

The key diagnostic criterion for EoE diagnosis is the increased number of eosinophils in the squamous epithelium of oesophageal biopsies⁶ (Fig. 1A and 1B). Eosinophil count along with morphologic alterations in the oesophageal epithelium and lamina propria, although *per se* non-diagnostic, support the diagnosis and provide information about the severity of the disease.

- **A peak eosinophil count (PEC)** of ≥ 15 intraepithelial eos/hpf (approximately 0.3 mm^2) is the consensus threshold for the histologic diagnosis of active EoE in the appropriate clinical context²⁰. Eosinophil count should be reported per 0.3 mm^2 to standardise its measurements. Table I provides the values to adjust and standardise the count for different field numbers of ocular types. Only intact intraepithelial eosinophils with clearly visible bilobed nuclei and coarse eosinophilic cytoplasmic granules should be counted^{9,21}. Eosinophils may also be present in the lamina propria; however, they should be excluded from the PEC because their presence

Table I. Conversion factor from eosinophils per hpf to eosinophils per 0.3 mm^2 based on the microscope's field number (FN).

Field Number (FN)	1 HPF 40x	Conversion factor to 0.3 mm^2
FN 18	0.159 mm^2	1.89 HPF
FN 20	0.196 mm^2	1.53 HPF
FN 22	0.237 mm^2	1.27 HPF
FN 23	0.260 mm^2	1.15 HPF
FN 24	0.283 mm^2	1.06 HPF
FN 25	0.310 mm^2	0.98 HPF
FN 26,5	0.345 mm^2	0.87 HPF

To express the peak eosinophil count per 0.3 mm^2 , the pathologist should first determine the count per hpf and then multiply this value for the conversion factor corresponding to the FN of the microscope.

- is not specific to EoE and can be observed in various other conditions, such as GERD, infections, or drug reactions, and even in asymptomatic individuals, particularly children⁹. Degranulated eosinophils, identified by extracellular granules lacking nuclei, and fragmented cells or nuclear debris should also be excluded from the count (Fig. 1C). However, their presence may support a diagnosis of active eosinophilic inflammation²². Thus, neutrophils (multilobulated nuclei, finer granules) or mast cells should not be misidentified as eosinophils. In EoE, neutrophil infiltration with the development of ulcers or erosions is unusual, unless complicated by GERD, pill oesophagitis, or infection⁹.
- **Eosinophilic abscesses (EAs)** are focal clusters of ≥ 4 eosinophils not separated by intervening epithelial tissue in the oesophageal epithelium^{23, 24} (Fig. 1D). Eosinophils also linearly align in the upper third of the epithelium, parallel to the epithelial surface. The '**eosinophil surface layering**' (ESL) is a linear alignment of ≥ 3 eosinophils in the upper third of the epithelium, parallel to the lumen¹⁰ (Fig. 1E). The formation of EAs is characteristic of EoE, as they are rarely observed in other oesophageal conditions^{23,25}. Their presence strongly supports the diagnosis and indicates active disease.
- **Dilated intercellular space (DIS)**, or spongiosis, refers to intercellular oedema in the oesophageal epithelium. It is observed as circumferential paracellular clefts in the oesophageal squamous epithelium, reflecting widened gaps between adjacent keratinocytes²⁴ (Figs. 1A, 1B, and 1E). These spaces often exhibit visible intercellular bridges, repre-

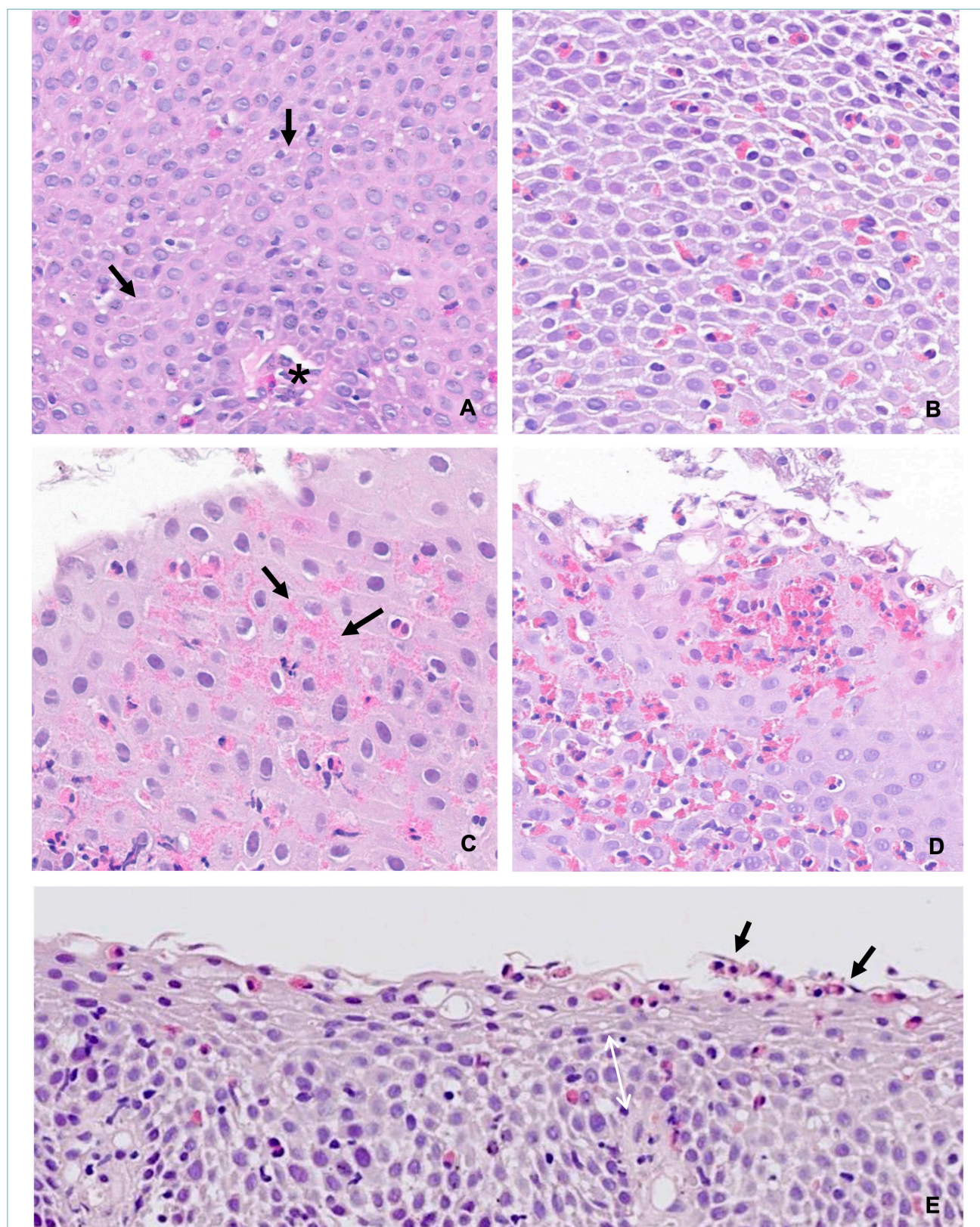


Figure 1. Inflammatory features of EoE. (A) Arrows indicate scattered intraepithelial eosinophils and mild spongiosis. The asterisk marks the lamina propria at the tip of a papilla, containing an eosinophil. (B) Numerous intraepithelial eosinophils are associated with diffuse and severe spongiosis. (C) Arrows indicate extracellular granules lacking nuclei, consistent with degranulation of eosinophils. (D) Eosinophilic abscesses characterised by a large cluster of eosinophils, without intervening epithelial cells. (E) Arrows indicate eosinophil surface layering. The white arrows suggests the involvement of severe spongiosis for almost the whole thickness of the epithelium and basal zone hyperplasia.

senting stretched desmosomal connections²⁴. DIS can be graded as small or large (as compared to the diameter of a small lymphocyte)²⁶. Small DIS is often limited to the lower half of the epithelium and must be differentiated from 'stretching' artefacts and intracytoplasmic vacuoles^{26,27} (Fig. 1A). Large DIS can involve the entire thickness of the epithelium (Fig. 1B).

- DIS indicate the disruption of epithelial tight junctions and barrier integrity, which are critical for maintaining oesophageal mucosal homeostasis²⁸. In EoE, DIS allows luminal antigens, allergens, and microbes to penetrate deeper into the epithelium, triggering immune activation and perpetuating eosinophilic infiltration²⁹.
- **Basal zone hyperplasia (BZH)** represents the reparative response of oesophageal epithelium to chronic injury and inflammation²⁸. Under normal conditions, the basal cell layer constitutes approximately 15% of the total epithelial thickness; however, in EoE, it frequently expands to more than 20-30%²⁴ (Figs. 1E, 2A, and 2B). This thickening results from increased proliferation of basal keratinocytes driven by inflammatory cytokines, particularly those released by eosinophils and other immune cells³⁰. Although BZH is not specific to EoE, in this context, its severity can increase and involve the entire epithelial thickness. It provides strong supportive evidence for EoE diagnosis when associated with marked eosinophilic infiltration. In cases where BZH is mild and confined to the lower third of the epithelium (typically < 30% of the epithelial thickness), proper biopsy orientation is essential for accurate evaluation. BZH also contributes to mucosal remodelling and compromises epithelial barrier function, thereby increasing susceptibility to antigen penetration and perpetuating chronic inflammation²⁴.
- **Superficial epithelial alteration (SEA)** is characterised by changes in the tinctorial properties of the oesophageal epithelium, manifesting increased eosinophilic staining (darker red appearance) of the surface epithelial cells¹⁰ (Figs. 2B and 2C). These alterations may be observed with or without an associated eosinophilic infiltrate. SEA is considered a marker of early epithelial injury, may reflect mucosal barrier dysfunction, and has been proposed as a marker of lamina propria fibrosis (LPF) (see below)³¹. Another potentially occurring feature is **dyskeratosis**, defined as aberrant or premature keratinisation of epithelial cells, indicating cellular stress or chronic injury¹⁰.

LPF is characterised by thickened connective tissue fibres replacing the physiologically thin and loosely

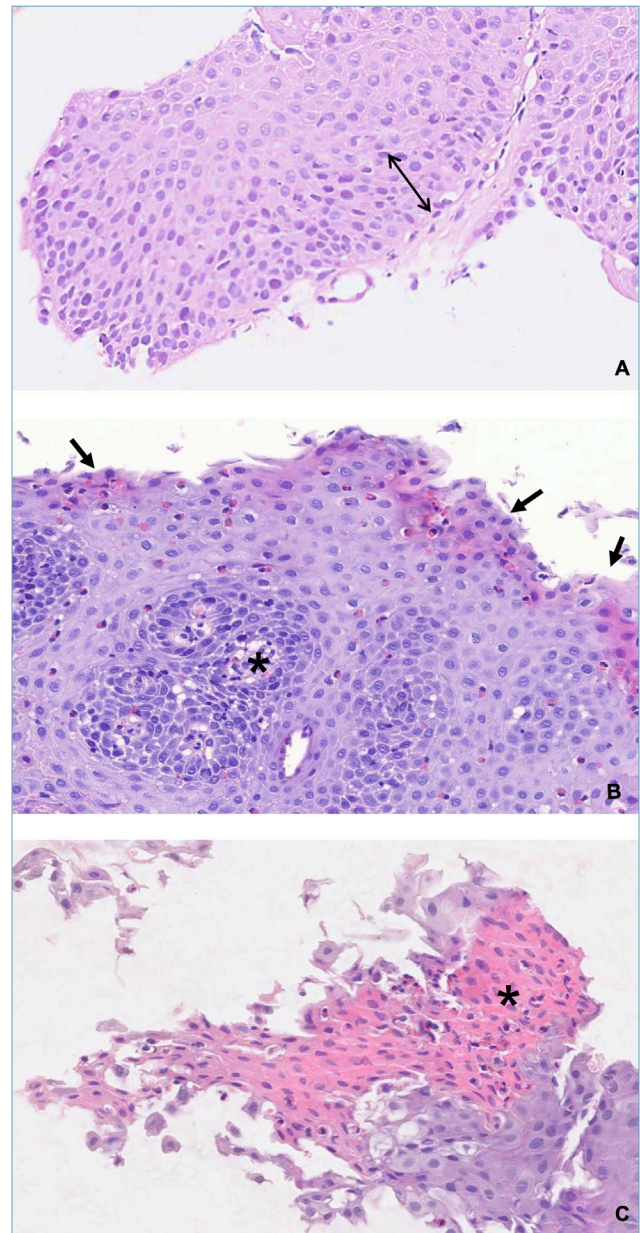


Figure 2. Basal zone hyperplasia and surface epithelial alterations. (A) Double arrow indicates the expansion of the basal zone, which extends to approximately 30% of the whole thickness of the epithelium. (B) Arrows indicate surface epithelial alteration, highlighted by the red appearance of epithelial cells. Asterisk shows the lamina propria within a papilla. (C) Asterisk indicates severe surface epithelial alteration.

arranged fibres. According to Collins et al. (2017), the diameter of normal fibres is smaller than that of a basal layer cell nucleus (Fig. 3A). They categorised the following types of fibres as abnormal: fibres that ap-

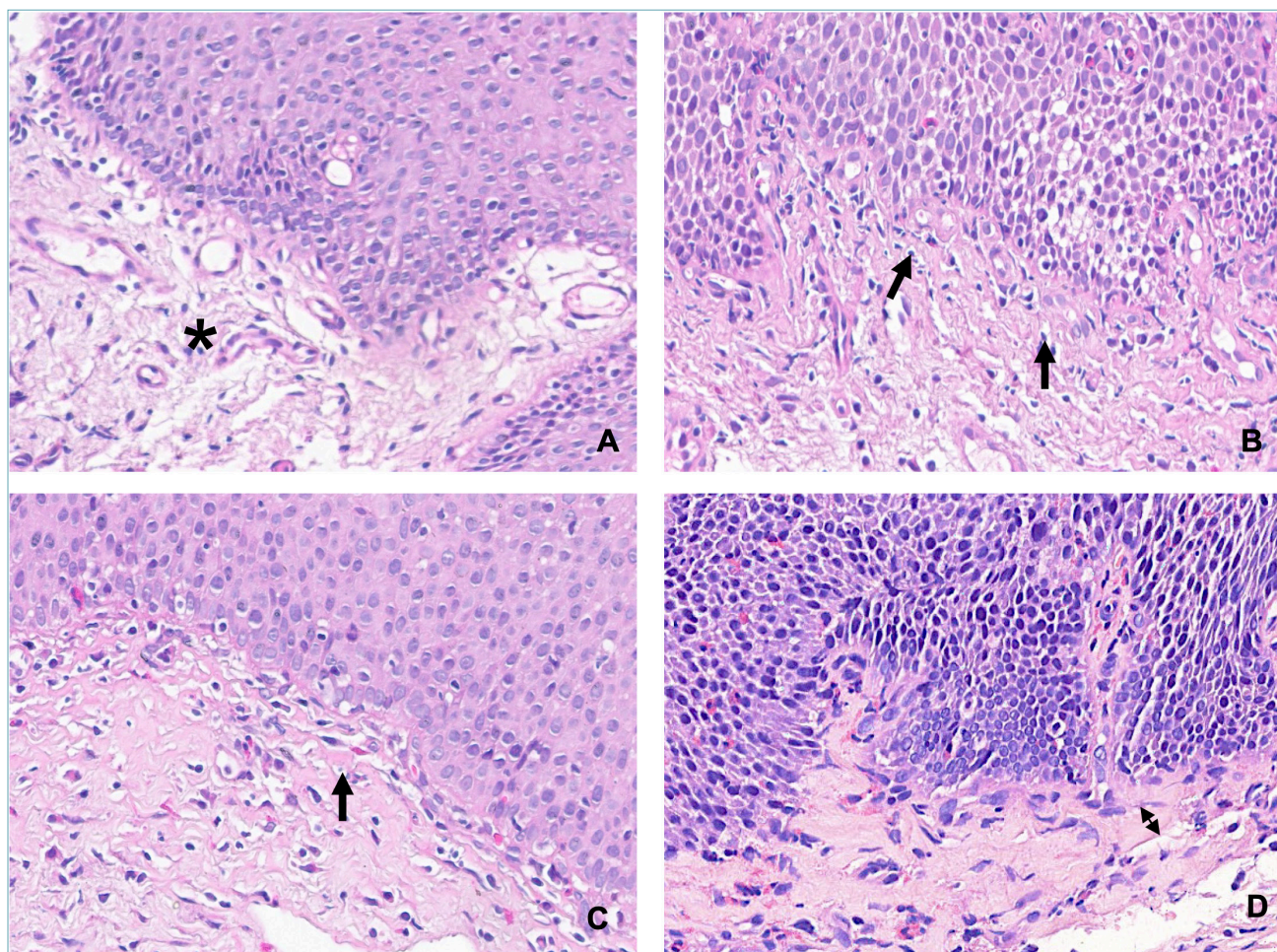


Figure 3. Lamina propria fibrosis. (A) The asterisk indicates normal lamina propria, characterised by a delicate network of thin and loosely arranged collagen fibres. (B) Arrows indicate fibres that appear cohesive beneath the epithelium. (C) Arrows indicate that the diameter of fibres has increased and is equal to the diameter of a basal layer cell nucleus (arrows). (D) Double arrow indicates that in this case of severe lamina propria fibrosis, the diameter of the fibres diameter is greater than that of a basal layer cell nucleus.

pear cohesive without an increased diameter; fibres with diameter equal to or greater than that of a basal layer nucleus (Figg. 3B, 3C, and 3D)¹⁰.

LPF is a hallmark of chronic and longstanding EoE. It results from persistent inflammation driving fibroblast activation and excess collagen deposition in the subepithelial connective tissue. This process causes thickening and stiffening of the oesophageal wall, leading to reduced distensibility and luminal narrowing; it clinically manifests as strictures, rings, and food impactions²⁴.

SCORING SYSTEMS

Besides reporting the morphologic changes described above, an assessment of their extent and degree is

fundamental to establish disease severity and to monitor the effect of therapy during follow-up. Thus, Collins et al. (2017) developed the EoEHSS, which is a validated tool that offers both grading and staging of the elementary histologic lesions associated with EoE (EA, ESL, BZH, DIS, SEA, LPF) in a 4-point scale (Tab II). The EoEHSS has demonstrated superior sensitivity to treatment effects compared to that of eosinophil count alone, and it exhibits correlation with symptoms scores. Although interobserver reliability is generally high among experienced gastrointestinal pathologists for most components of the EoEHSS, reproducibility is lower among less-experienced readers³². Moreover, the suboptimal orientation of endoscopic biopsies often prevents reliable evaluation of certain parameters,

Table II. Eosinophilic Esophagitis Histologic Scoring System (EoEHSS) (Collins et al. 2017, mod.).

Feature	How to evaluate	GRADE SCORE				STAGE SCORE			
		0	1	2	3	0	1	2	3
BZH	% total epithelial thickness occupied by BZH	none	>15% ; <33%	>33% ; <66%	>66%	none	Any grade>0 in <33% of epithelium*	Any grade >0 in 33-66% of epithelium*	Any grade>0 in >60% of epithelium*
EI	No. Eo/0,3mm ²	0	<15	15-59	>60	0			
EA	No. Eo forming the abscess	0	4-9	10-20	>20	0			
SL	No. Eo linearly allined on the epithelial surface, parallel to the lumen	0	4	5-10	>10	0			
DIS	Degree of magnification required to see the intercellular bridges	0	400x	200x	100x	0			
SEA	Darker red staining of surface epithelial cells with or without associated Eo	0	Present without Eo	Present with Eo	Shed epithelium with eosinophils's exudate	0			
Dysk	No./0,3mm ²	0	1	2-5	>5	0	Any grade>0 in <33% of lamina propria	Any grade >0 in 33-66% of lamina propria	Any grade>0 in >66% of lamina propria
LPF	Degree of fibre thickening	Not present	Cohesive, not demarcated fibers	Fibre diameter equals the diameter of a basal cell nucleus	Fibre diameter exceeds the diameter of a basal cell nucleus	Not present			

Modified from Collins et al. 2017.

BZH, basal zone hyperplasia; EI, eosinophil inflammation; EA eosinophil abscess; Eo: eosinophils; SL, surface layering; DIS, dilated intercellular space; SEA, superficial epithelial alteration, Dysk, dyskeratotic epithelial cells, LPF, lamina propria fibrosis.

The maximum possible grade or stage score for each biopsy is 24

* Stage score for EI is based on the amount of the biopsy that exhibited the threshold value for EoE diagnosis (i.e. PEC>15/0,3mm²)

such as BZH, and the absence of lamina propria in most biopsies prevents its evaluation. Despite these limitations, EoEHSS remains a validated histologic

scoring system that offers a more complete picture of overall histologic severity, thus helping to monitor the clinical course of patients during follow-up.

Recently, to further enhance standardisation and support longitudinal disease management, the I-SEE was introduced⁷. I-SEE integrates clinical, endoscopic, and histologic data to assess both inflammatory and fibrostenotic features. Oesophageal eosinophilia, categorised as 15–60 Eos/hpf or > 60 Eos/hpf, remains the central marker of inflammation. Additional features such as BZH and LPF are recognised as markers of oesophageal wall remodelling. The presence of SEA and dyskeratotic epithelial cells are considered surrogates of LPF, when the latter is not available in the biopsy.

DIFFERENTIAL DIAGNOSIS

EoE must be distinguished from other causes of oesophageal eosinophilia, such as drug reactions, connective tissue disorders, and infections. These alternative diagnoses should be considered in the absence of a typical clinical and endoscopic presentation, and their identification relies primarily on clinical information. In the paediatric population, differentiation between EoE and GERD can be particularly challenging, owing to overlapping clinical manifestations and histologic features. Notably, intraepithelial eosinophils are detected in up to 50% of GERD cases²⁶. Thus, a comprehensive evaluation, integrating clinical, endoscopic, and histologic findings, is essential to establish an accurate diagnosis.

EoE VARIANTS

Growing evidence suggests that EoE may represent only the tip of the iceberg within a broader spectrum of Th2-mediated oesophageal disorders with overlapping clinical and endoscopic manifestations but involving different inflammatory cell types, such as B or T lymphocytes and mast cells.

The term EoE-like disease was first introduced by Straumann in 2016³³, and since then, several EoE variants have been described³⁴. These include:

- *EoE-like oesophagitis*: defined as the presence of <15 eosinophils/0.3 mm², with features of epithelial damage, such as DIS and BZH.
- *Lymphocytic oesophagitis*: defined as the presence of a lymphocyte-predominant intraepithelial inflammation mainly in peripapillary fields, associated with marked peripapillary spongiosis without intraepithelial granulocytes. The diagnostic cut-off for lymphocytic oesophagitis has been debated for years; in 2017, Rubio proposed > 40 intraepithelial lymphocytes/hpf (>65 lymphocytes/0.3 mm²)³⁵, which was later confirmed by an expert panel in 2024³⁶.
- *Non-specific oesophagitis*: defined as the presence of intraepithelial lymphocytes not fulfilling the

numerical and distributional criteria of lymphocytic oesophagitis, and without eosinophils (neutrophils can be observed).

- *Mast-cell oesophagitis*: a recently described entity, wherein patients with oesophageal symptoms, normal endoscopy, and normal or non-specific histology display numerous intraepithelial mast cells (> 60/mm², equivalent to > 18/0.3 mm²) identified by tryptase staining³⁷. Although a clear correlation has not been established between mast-cell density and clinical presentation, there is growing interest in the potential role of mast cells in oesophageal disease, given their well-known function in allergy-mediated immune responses.

Long-term follow-up has shown that approximately one-third of patients with EoE variants may transition between subtypes or progress to classical EoE³⁸. However, additional evidence is needed to clearly define these variants and their clinical significance.

RECOMMENDATIONS FOR THE PATHOLOGY REPORT

As previously mentioned, 6 is the ideal number of biopsies for an accurate diagnosis, taken from ≥ 2 different regions of the oesophagus, preferably including the proximal, middle, and distal segments. Moreover, < 4 specimens reduce diagnostic sensitivity and are considered insufficient/inadequate if EoE is not identified. In such cases, the pathologist should specify that the material is not adequate for diagnostic purposes. However, if EoE is evident in the available tissue, the sample should still be evaluated, and a diagnosis should be rendered accordingly.

Given that the diagnosis of EoE requires a multidisciplinary approach and exclusion of other potential causes of oesophageal eosinophilia (see above), pathology reports should state that the findings are 'compatible with EoE' rather than 'diagnostic of EoE.' Importantly, intraepithelial eosinophils are not normally present in oesophageal biopsies^{39–40}; thus, any degree of eosinophilic infiltration should be noted. This is particularly significant when assessing follow-up biopsies in patients undergoing treatment for EoE. In this context, a PEC < 15 Eos/hpf (0.3 mm²) is generally considered the cut-off for histologic disease control⁸, whereas a PEC < 6 Eos/hpf (0.3 mm²) indicates histologic remission⁷. Moreover, considering that PEC value is associated with EoE severity, reporting the exact number of PEC/0.3 mm² is advisable⁷.

Thus, in both diagnostic settings and during follow-up, besides calculating PEC/0.3 mm², accompanying histological features must be described, graded, and staged, possibly by applying the EoEHSS.

A schematic structure of the report is shown in Table III.

Table III. Histology report – Suggested structure of the histology report.

Pathology report
Sample description
Number of biopsies collected from the proximal/middle/distal oesophagus
Clinical and endoscopic information
• Clinical history
• Eosinophilic Esophagitis Endoscopic Reference Score (EREFS)
• Ongoing therapy
• Prior diagnosis
Histological description
Essential
• Peak eosinophil count (PEC) (Eos/0.3 mm²).
- It is desirable to report the exact number of Eos/0.3 mm ² .
- It is essential to report at least the following cut-off:
- ≤6 Eos/0.3 mm ² , <15 Eos/0.3 mm ² , 15-60 Eos/0.3 mm ² >60 Eos/0.3 mm ²
• Morphologic description of additional histologic features:
- Eosinophilic abscesses (present/absent)
- Eosinophil surface layering (present/absent)
- Dilated intercellular spaces (to be graded as small/large)
- Basal zone hyperplasia (to be graded as <30% or >30% of the epithelial thickness)
- Superficial epithelial alterations (present/absent)
- Lamina propria fibrosis (present/absent)
Desirable:
• EoE Histologic Scoring System (EoEHSS) sec. Collins 2017
Diagnosis
Samples are inadequate for diagnostic purposes
Histology do not support the diagnosis of EoE
Histology is compatible with the diagnosis of EoE

Conclusions

This document underlines the importance of histologic evaluation in the diagnosis and management of EoE, addressing the critical need for standardisation in EoE histological reporting. The use of the PEC/0.3 mm² reporting criterion, rather than eos/hpf, for eosinophil counting is consistent with the recent recommendations, and it enables more reliable comparisons of outputs from different microscopes. The emphasis on reporting other inflammatory and fibrostenotic features beyond eosinophil count reflects the complex pathophysiology of EoE and may provide additional insights into disease progression and treatment response.

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Conflicts of Interest.

MF: None declared.

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LM: None declared.

MDA: None declared.

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AV: Has served as a consultant in Advisory Boards for Amgen, BeOne, MSD Italia, and Sanofi.

VA: None declared.

MM: Consultant for Sanofi.

SO: Has served as a speaker for Sanofi/Regeneron, Recordati, Alfasigma, and Bristol Myers Squibb, Medtronic; has served as an advisory board member for AstraZeneca, Alfasigma, Dr. Falk, Recordati, Sanofi/Regeneron, and Medtronic.

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Authors' Contributions

VA and MM drafted the initial manuscript. CG, MF, EVS, and SO revised the initial draft of the manuscript. All authors approved the final version of the manuscript.

Ethical Consideration

This study did not involve human participants or pa-

tient data and therefore did not require ethical approval.

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