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EDITORIAL

Changes in the esophageal mucosa of patients with non erosive reflux disease: How far have we gone?

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Abstract

The normal esophageal mucosa creates a protective epithelial barrier that constrains the acidic reflux in the esophageal lumen. Microscopic findings and functional studies indicate that this barrier might be impaired in patients with non erosive reflux disease (NERD) but not in patients with functional heartburn (FH). Whereas endoscopy and pH monitoring are the most important diagnostic tools in the diagnosis of NERD, recent studies suggest that esophageal biopsies might have a complementary role. Particularly in the differential diagnosis between NERD and FH, the application of histological severity scores showed very promising results. Further evaluation of the scores could lead to routine application of histology in specific NERD populations.

Key words: Esophageal mucosa; Non erosive reflux disease

Core tip: The normal esophageal mucosa creates a protective epithelial barrier that might be impaired in patients with non erosive reflux disease (NERD). Whereas endoscopy and pH monitoring are the most important diagnostic tools in the diagnosis of NERD, recent studies suggest that esophageal biopsies might have a complementary role. Particularly in the differential diagnosis between NERD and functional heartburn, the application of histological severity scores showed very promising results. Further evaluation of the scores could lead to routine application of histology in specific NERD populations.

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INTRODUCTION

An increased prevalence of gastroesophageal reflux

disease (GERD) has been observed in developed countries and symptoms suggestive of GERD (heartburn and/or regurgitation) are a common reason for consultation[1,2]. The spectrum of GERD includes erosive reflux disease (ERD) characterized by the presence of esophagitis and non-erosive reflux disease (NERD) characterized by the absence of endoscopically visible lesions and the presence of abnormal pH monitoring. Patients with heartburn, normal endoscopy and normal pH monitoring are classified, according to the Rome Ⅲ criteria as functional heartburn patients (FH)[3].

NERD patients represent up to 60% of all patients with reflux symptoms, but the mechanisms involved in the pathogenesis of NERD are complex and multifactorial[3]. The effects of gastric reflux on the esophageal mucosa of NERD patients are still incompletely understood. It is well known that the normal esophageal mucosa creates an effective barrier that constrains the acidic refluxate in the esophageal lumen[4]. Microscopic changes in the esophageal mucosa indicate that this barrier might be impaired in patients with NERD suggesting a possible role in the pathogenesis of the disease[5].

The role of histology in the diagnosis of NERD is very limited, keeping in mind that individual histological markers related to GERD have shown poor diagnostic value[6]. However, recent studies indicated that a histological score, based on a combination of histological parameters might be significantly associated with patients' symptoms and esophageal acid exposure and could thus contribute not only to the diagnosis of NERD but also to the differential diagnosis between patients with NERD and patients with FH[7,8].

NORMAL MUCOSA

Esophageal epithelium acts as a barrier that constrains the noxious acidic refluxate into the esophageal lumen and separates it from the esophageal nociceptors. It is a multilayer, non keratinized, stratified squamous epithelium and is consisted of three layers: closest to the lumen is the stratum corneum, underneath lies the stratum spinosum and finally towards the serosa lies the stratum basale or stratum germinativum[4].

Between the cells of the esophageal epithelium there are strong intercellular junctions that create an effective mucosal barrier and limit the paracellular ion diffusion; the tight junctions, the adherens junctions and the desmosomes[4]. Tight and adherent junction proteins encircle the cells and seal the barrier that separates the lumen from the intercellular space. Mainly claudin proteins and occludin contribute to the formation of tight junctions while the main protein in adherent junctions is E-cadherin. Desmosomes contribute to structural integrity of the mucosa by keeping the close apposition of the adjacent cells[4,5].

ESOPHAGEAL MUCOSA IN NERD

The most extensively studied finding in the esophageal epithelium of NERD patients is the presence of dilated intercellular spaces (DIS). It has been proposed as a mechanism of impaired mucosal integrity and increased acid perception[9]. Acid perfusion in the esophagus of healthy volunteers caused dilation of intercellular spaces in initially normal epithelium[10]. Increased mucosal permeability due to DIS could permit the acidic fluid reach the sensitive esophageal nociceptors that terminate in the intercellular space[11-13]. Moreover, an experimental study showed that not only acidic but weakly acidic solutions containing bile acids could also provoke increased DIS[10]. It has been found that in NERD patients the mean intercellular space diameter in distal esophagus is threefold higher compared with controls[9]. PPI treatment resolves symptoms and normalize DIS[14], whereas DIS were still increased in refractory heartburn patients despite double PPI dose[15]. In parallel with DIS, an upregulation of specific desmosomal and tight junction proteins has been shown. This change could represent a mucosal reaction towards recovery of the epithelial barrier[16,17].

Hyperplasia of the basal layer of the epithelium and elongation of the papillae that are more prevalent in the mucosa of NERD patients compared to healthy controls and functional heartburn patients, are other interesting findings[6]. It has been proposed that these findings represent a regenerative response to reflux induced mucosal damage[6]. Comparing these markers to DIS, DIS shows higher sensitivity and specificity for the diagnosis of NERD, although it is found present in up to 30% of asymptomatic healthy subjects[6,12]. Thus, the lack of specificity and sensitivity make these markers of limited use for the diagnosis of NERD.

The functional integrity of the esophagus has been assessed *in vitro* and *in vivo.* In vitro assessment is made with the use of the Ussing chamber technique which includes the placement of an esophageal mucosa specimen in an aperture that separates two solutions. The transepithelial resistance (TER) is then calculated. TER is indicative for the functional integrity of the mucosal barrier that separates the luminal from the basal side of the epithelium[5]. When esophageal biopsies were exposed to acidic solutions the impairment in integrity as measured by TER was greater in NERD patients compared to controls, indicating a defective mucosal barrier[18]. *In vivo* functional integrity of the esophagus has been evaluated with the application of multichannel esophageal impedance catheter[19]. It has been shown that NERD patients had lower baseline esophageal impedance compared to FH patients and controls, thus supporting the hypothesis of increased mucosal permeability to ions and therefore increased sensitivity to acid[20,21] . These findings suggest that an easy

Table 1 Histological criteria for the assessment of microscopic lesions described by Yerian *et al*[28]

Criterion	Definition and method of assessment (magnification)	Severity score
Basal cell hyperplasia	Measure basal cell layer in μm and express as a proportion of total epithelial thickness (× 10)	0 (absent < 15%), 1 (15%-30%), 2 (> 30%)
Papillary elongation	Measure papillary length in μm and express as a proportion (%) of total epithelial thickness (× 10)	0 (absent < 50%), 1 (50%-75%), 2 (> 75%)
Dilated intercellular spaces	Include irregular round dilations and diffuse widening of the intercellular space (× 40) Small intercellular space= diameter < 1 lymphocyte Large intercellular spaces = diameter ⩾ 1 lymphocyte	0 (⩽ 5 small), 1 (⩾ 6 small and ⩽ 5 large) 2 (⩾ 6 large)
Intraepithelial eosinophils	Count cells in the most affected power field (× 40)	0 (0 cells in one high power field)
Intraepithelial neutrophils		1 (1-2 cells), 2 (> 2 cells)
Intraepithelial mononuclear cells	Count cells in the most affected power field (× 40)	0 (0-9 cells) 1 (10-30 cells), 2 (> 30 cells)
Erosions	Assess as presence of at least one of the following: necrosis, granulation tissue or fibrin with neutrophils (× 10)	0 (absent), 1 (present)
Healed erosions	Assess as presence of granulation tissue covered by thinned regenerative epithelium (× 10) in the absence of necrosis, fibrin, and neutrophils	0 (absent), 1 (present)
Combined severity score	Sum of lesion severity scores divided by the number of lesions assessed (excludes intraepithelial monuclear cells and neutrophils, and erosions/healed erosions) 0-0.25 normal mucosa, 0.5-0.75 mild esophagitis ⩾ 1 severe esophagitis	

Biopsies were taken from the Z-line and at 2 cm above it.

software aided assessment of baseline impedance could add diagnostic information in the routine application of pH-impedance measurements.

Finally, an immune mediated mechanism has also been investigated in the pathogenesis of NERD. It has been suggested that reflux might stimulate proinflammatory cytokine production (*e.g.*, interleukin 8) by the esophageal epithelium that mediates damage of the esophageal tissue[22]. IL-8 and IL-1β have been found upregulated in the esophageal mucosa of NERD patients when compared to controls[23,24]. Treatment with lansoprazole reduced the mucosal levels of both mRNA and protein IL-8 levels[25]. Additionally, upregulation of proteinase-activated receptor-2 (PAR-2) which has been demonstrated to induce proinflammatory and neuroinflammatory effects has also been found in NERD patients compared to controls[26] . In esophageal biopsies infiltration of the mucosa with inflammatory cells is more prevalent in NERD compared to FH patients and controls[6-8].

APPLICATION OF HISTOLOGICAL SCORES

The poor diagnostic value of individual histological markers has led to the application of histological scores in the diagnosis of NERD. These scores take into account a combination of histological parameters associated with extensive acid reflux and have opened new hopeful perspectives on the role of esophageal biopsies.

Recently a large international group of pathologists reached a consensus regarding the microscopic lesions in esophageal biopsies of patients with GERD that could provide the histological diagnosis of microscopic esophagitis. Individual lesions were assessed: basal cell hyperplasia, papillary elongation, DIS, intraepithelial eosinophils, neutrophils and mononuclear cells. After that, a combined histological severity score was obtained by summing up lesion scores for each of the above parameters (Table 1)[27,28]. Evaluation of the score showed good correlation with patients' reflux symptoms as well as good interobserver agreement[29].

Savarino *et al*[7] used light microscopy and applied the histological score in esophageal biopsies of pHmetry defined NERD and FH patients as well as in healthy controls (Table 2). Application of the score was able to differentiate patients with NERD from those with FH with an accuracy of 79%, a sensitivity of 74% and a specificity of 86%, whereas no difference was found in the prevalence of microscopic esophagitis between FH patients and healthy controls. Furthermore, in GERD patients refractory to PPIs application of a similar histological score was able to discriminate NERD and FH patients with sensitivity 0.85, specificity 0.64, positive predictive value 0.71 and negative predictive value 0.8 (Table 3). Overall patients with NERD were differentiated from patients with FH with high statistical significance ($P < 0.001$)[8].

Biopsy sampling and application of histological scores is a relatively safe and inexpensive procedure in a disease with a massive financial impact[30]. However, limitations for the use of histological scores do exist mainly regarding the position where the biopsies should be taken. It has been shown that the distribution of the microscopic findings is patchy and

Table 2 Histological score applied by Savarino *et al*[7]

Criterion	Definition and method of assessment (magnification)	Severity score
Basal cell hyperplasia	Measure basal cell layer in μm and express as a proportion of total epithelial thickness (× 10)	0 (absent < 15%), 1 (15%-30%), 2 (> 30%). Z line 1 (> 20%)
Papillary elongation	Measure papillary length in μm and express as a proportion (%) of total epithelial thickness	0 (absent < 50%), 1 (50%-75%), 2 (> 75%) Z line 1 (> 66%)
Dilated intercellular spaces	Include irregular round dilations or diffuse widening of the intercellular space (× 40) Small intercellular space= diameter < 1 lymphocyte Large intercellular spaces= diameter ⩾ 1 lymphocyte	0 (⩽ 5 small), 1 (⩾ 6 small and ⩽ 5 large) 2 (⩾ 6 large)
Intraepithelial eosinophils	Count cells in the most affected power field (× 40)	0 (0 cells in one high power field) 1 (1 cell), 2 (> 1 cells)
Intraepithelial neutrophils	Count cells in the most affected power field (× 40)	0 (absent), 2 (present)
Erosions/ necrosis	Assess as presence of at least one of the following: necrosis, granulation tissue or fibrin within neutrophils (× 10)	0 (absent), 2 (present)
Combined severity score	Sum of lesion severity scores divided by the number of lesions assessed. Erosions/necrosis are not counted for the global score Positive for microscopic esophagitis when the value was ⩾ 0.35	

Biopsies were taken from the squamous epithelium side of the squamocolumnar junction and at 2 cm above it.

Table 3 Histological score applied by Kandulski *et al*[8]

Type of Lesion	No changes	Mild changes	Moderate changes	Severe changes
Basal cell hyperplasia	0	1	2	3
Papillary elongation	0	1	2	3
Dilated intercellular spaces	0	1	2	3
Inflammation	0	1	2	3
Sum score	A cut-off value > 5 points was applied for discrimination between NERD and FH			

Biopsies were taken 3-5 cm above the gastro-oesophageal junction.

varies significantly according to the distance from the squamocolumnar junction and to the position of the biopsy. Mucosal changes occur more frequently closer to Z line and in the 3 o'clock quadrant[31]. Therefore a common biopsy protocol is necessary. Furthermore, the precise assessment of GERD related microscopic lesions severity which is necessary for the scoring could be troublesome or subjective although these lesions are often easily recognized. Hence adjustment to a consensus with strict detailed criteria is necessary[28].

Outcome studies in NERD patients investigating a possible association between histological score and the response to pharmacological therapies or to fundoplication would be noteworthy. A strong association could enhance the role of biopsies before therapeutic decisions for these patients. A multicenter study that included both patients with NERD and erosive esophagitis showed that baseline histological score could not be a predictor of treatment failure either for esomeprazole or fundoplication. However a subgroup analysis only for NERD patients has not been performed. An interesting result of this study suggesting a possible role of histology in the long term follow up of GERD patients is the significantly lower score found in patients with treatment induced remission compared to treatment failures[32].

Another application of histological score could be the evaluation of the natural history of NERD patients especially these with a high severity score. It has been hypothesized that chronic inflammation and continued epithelial injury could have important role in the pathogenesis of Barrett esophagus[33,34], thus a long term study including a second upper endoscopy of patients with a high severity score could estimate a possible higher incidence of Barrett esophagus among these patients.

Furthermore, histological findings could be of value in the differential diagnosis between NERD and FH especially in specific subgroups: NERD patients with borderline findings in 24 h pH metry, patients reluctant or unable to undergo 24 h pH monitoring, patients with suspicion that catheter intolerance has significantly influenced the diagnostic value of the test.

CONCLUSION

The normal esophageal mucosa creates a protective epithelial barrier that constrains the acidic reflux in the esophageal lumen. Microscopic findings and functional studies indicate that this barrier might be impaired in patients with NERD but not in patients with FH. Whereas endoscopy and pH monitoring are the most important diagnostic tools in the diagnosis of NERD, recent studies suggest that esophageal biopsies might have a complementary role. Particularly in the differential diagnosis between NERD and FH, the application of histological severity scores showed very promising results. Further evaluation of the scores could lead to routine application of histology in specific

NERD populations.

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