

Review

Minimal changes in reflux esophagitis: red ones and white ones

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Minimal change esophagitis is commonly accepted as part of the spectrum of reflux esophagitis in Japan as well as in many reflux esophagitis classification systems. However, the Los Angeles system excludes minimal changes as a sign of reflux esophagitis because of low interobserver agreement. The high prevalence of minimal change esophagitis suggests that many endoscopists can recognize such findings in their patients' esophagi. However, we do not have a clear definition of minimal changes, which requires proven interobserver agreement, histological evidence, and response data to therapeutic intervention. Furthermore, erythematous changes (red ones) and acanthotic changes (white ones) are not distinguished in the definition of minimal change used in Japan. It is time to clarify such issues.

Key words: reflux esophagitis, endoscopic classification, minimal change

Introduction

A decreased prevalence of *Helicobacter pylori* infection among the Japanese population, especially among the elderly population, has led to an increase in the prevalence of gastroesophageal reflux disease (GERD)/reflux esophagitis in Japan, along with changes in dietary habits to more fat consumption.¹ With the increased prevalence of GERD and reflux esophagitis, more and more attention has been paid to the endoscopic diagnosis of reflux esophagitis. A recent nationwide survey among patients having an endoscopic procedure as the initial approach showed that 33% had minimal change or erosive esophagitis,² among which half had minimal change esophagitis.

There are many grading systems for endoscopic severity of reflux esophagitis. Among the various systems, the Los Angeles (LA) classification system^{3,4} is most widely accepted. In Japan, a modified LA system, with the added grades M and N, is widely accepted^{5,6} (Table 1). In the modified LA system, grade M is defined as "Erythema without sharp demarcation, whitish turbidity, and/or invisibility of vessels due to these findings." This concept is an extension of the Japanese classification system, developed by the Japanese Study Group for the Esophageal Disorders, both the original system and the recently modified one^{7,8} (Table 2).

How minimal changes are recognized in classification systems of reflux esophagitis

Minimal changes such as erythema, increased vascularity, friability, and edema were considered by the International Working Group for Classification Oesophagitis (IWGCO) during the development of the Los Angeles classification system. They found that minimal changes of erythema or increased vascularity (i.e., "red ones") could be evaluated more consistently than such minimal changes as friability and edema. Among experienced endoscopists, kappa values for the detection of red ones range from 0.6 to 0.8, whereas they range from 0.35 to 0.45 for detection of non-red ones; among inexperienced endoscopists, however, they are less than 0.4 for red ones and 0.19 for non-red ones.³ Because inexperienced endoscopists have difficulty recognizing these lesions, this group excluded minimal changes from the diagnostic criteria for reflux esophagitis.

For similar reasons, some other classification systems exclude such minimal changes from the classification criteria for reflux esophagitis, but many include them (Table 2). Among the published classification systems, only the Japanese system includes findings of "whitish

Table 1. Los Angeles classification system with Japanese modifications⁵

Grade	Description
N	Normal mucosa
M	Minimal changes to the mucosa, such as erythema and/or whitish turbidity
A	Nonconfluent mucosal breaks <5 mm in length
B	Nonconfluent mucosal breaks >5 mm in length
C	Confluent mucosal breaks <75% circumferential
D	Confluent mucosal breaks >75% circumferential

Table 2. Classification systems for endoscopic severity of reflux esophagitis

Descriptors for mucosal findings	LA system (revised) Lundell et al. (1999) ⁴	LA system, Japanese modification. Hoshihara (1996) ⁶	JSED (1973) ⁷	JSED, Tokyo 96 System. Kouzu et al. (1997) ⁸	Savary and Miller (1978) ⁹	Sonnenberg et al. (1982) ¹⁰
Normal	/	N: Normal mucosa	/	0: Normal	/	0: No esophagitis
Minimal changes ^a	/	M: Erythema and/or whitish turbidity	1: Discoloration (erythema, and or whitish turbidity)	1: Erythema and/or whitish turbidity, including those who have lesions unstained by iodine spray	I: One or more nonconfluent lesions with erythema and edema	/
Small erosive lesion(s)	A: Nonconfluent MB(s) <5 mm, each one on a single fold	A: Nonconfluent MB(s) <5 mm, each one on a single fold	2: Erosive and/or ulcerative type (mucosal breaks)	2: Nonconfluent erosions/ulcers located within the distal 5 cm	II: Noncircumferential multiple erosive and/or erythematous lesions	I: Mild, isolated erosions
Bigger erosive lesion(s) but not confluent	B: Nonconfluent MB(s) ≥5 mm, each one on a single fold	B: Nonconfluent MB(s) ≥5 mm, each one on a single fold		3: Nonconfluent erosions/ulcers located 5–10 cm proximal to the EGJ, or confluent but not circumferential		
Mild confluent erosive lesions	C: Circumferential MB(s) <75%	C: Circumferential MB(s) <75%				II: Severe, confluent circumferential erosions
Mostly circumferential erosive lesions	D: Circumferential MB(s) >75%	D: Circumferential MB(s) >75%		4: Erosions/ulcers exceeding 10 cm proximal from EGJ, or circumferential	III: Circumferential erosive lesions	
Ulceration	/	/			IV: Columnar epithelium, ulcer(s), stricture(s)	III: Deep ulcers, stenosis, and/or columnar-lined esophagus
Complication(s)	/	/	/	/		
Main minimal changes		Erythema, turbidity	Erythema, blurring	Erythema, blurring		
Main Lesions	Mucosal break	Mucosal break	Mucosal break	Erosion/Ulcer	Erosion	Erosion

LA, Los Angeles; JSED, Japanese Society for Esophageal Disease; MB, mucosal break; SCJ, squamocolumnar junction; EGJ, esophagogastric junction; —, ulceration is included in other grades; /, such findings not described by the classification system

^aMinimal changes are included in the spectrum of reflux esophagitis, but the descriptions are not consistent

turbidity”; the other systems list only red ones. Red ones are well recognized by experienced endoscopists, and also by inexperienced endoscopists although with a lower level of agreement, whereas non-red ones (i.e., “white ones”) are not well recognized.

In Japanese studies, minimal change esophagitis is recognized quite frequently (50%–70%) among pa-

tients with reflux symptoms,^{2,18} and similar findings have been published from Europe.¹⁹

These data suggest that red and white minimal changes are recognized consistently well by experienced endoscopists. However, we do not know whether all endoscopists are aware of the difference between red ones and white ones.

Knuff et al. (1984) ¹¹	Hetzel et al. (1988) ¹²	Johnson et al. (1989) ¹³	Bate et al. (1990) ¹⁴	Tytgat et al. (1990) ¹⁵	MUSE system, erosions Armstrong et al. (1991) ¹⁷	Bytzer et al. (1993) ¹⁶
0: Normal	0: Normal mucosa with no abnormalities	0: Normal mucosa	0: Normal esophageal mucosa	0: No evidence of reflux-induced damage	E0: absent	0: No mucosal abnormalities
I: Hyperemia, patchy and/or linear	I: Erythema or hyperemia, but no macroscopic erosion	I: Nonconfluent erythema or exudate	I: Erythema and friability with spontaneous contact bleeding	I: Mild, patchy, diffuse erythema at SCJ. Minor friability, loss of shininess, no MB	/	1: Diffuse erythema, edema, mucosal , friability isolated erythema
II: Hyperemia, granularity and/or friability						
III. Erosions	II: Superficial ulceration or erosions, <10% of the distal 5cm esophagus	II: Confluent, noncircumferential erosive and exudative lesions	II: Isolated round or linear erosions at 2cm of distal esophagus, but not the entire circumference	II: Superficial erosions of red dots or streaks, <10% of 5cm distal esophagus. III: Confluent, non-circumferential erosions, <50% of over all mucosa of distal 3cm	E1: Erosion(s) at one fold	2: Fibrin covered, noncircumferential erosions
	III: Superficial ulceration or erosions, >10%–50% of the distal 5cm esophagus IV: Deep ulceration anywhere in the esophagus, or confluent erosion of >50% of the distal 5cm esophagus	III: Circumferential erosive and exudative lesions	III: Erosions over more than 2cm of the distal esophagus or entirely circumferential	IV: Circumferential or exudative lesions at SCJ, regardless of the extent along the distal esophagus	E2: Erosions at ≥ two folds E3: Circumferential erosions	3: Entirely circumferential confluent erosions or ulceration
IV: Stricture or frank ulcer	/	/	IV: Frank benign ulcer	V: Deep ulceration	/	
	/	/	V: Stricture	VI: Stricture	/	4: Stricture or columnar-lined
Hyperemia	Erythema	Erythema	Erythema, friability	Erythema, friability		epithelium Erythema, edema, friability
Erosion	Erosion/Ulcer	Erosion	Erosion	Erosion	Erosion	Erosion

Are minimal changes part of the spectrum of reflux disease?

Minimal changes are found in the majority of heartburn patients in studies using systems that have minimal changes as part of the spectrum of reflux disease.^{2,5,18,19} This suggests that minimal changes can be considered part of the spectrum of acid reflux disease. In a nationwide survey in Japan, endoscopic findings of minimal changes were also analyzed in relation to the presence of hiatal hernia; minimal changes were found in 10% of patients without hiatal hernia and in 25% of patients with hiatal hernia regardless of the severity of the hernia.²⁰ Does this finding indicate that minimal changes are part of the reflux disease spectrum? In Japanese studies in which a high prevalence of minimal changes were found among GERD patients, findings of red ones and white ones are both classified into just one category. Is this way of analysis right?

Historical views on minimal changes

Many studies have described minimal changes (see Table 2), but many of these descriptions are only of red ones, that is, erythema, red patches, and increased vascularity. In the original Savary-Miller classification system,⁹ erythema was defined as a sign of reflux esophagitis (grade I esophagitis), but erythema was corrected to erosions in later revisions. In Japan, the Japanese Society for Esophageal Disorders (JSDE) defined a grading (or staging) system in 1973,⁷ which was modified in 1996,⁸ but both versions included minimal changes. In each, stage I discoloration, defined as “erythema and/or whitish turbidity of the esophageal mucosa, and reduced visibility of vessels due to erythema and/or whitish turbidity,” indicated that the endoscopic appearance of the esophageal mucosa was not normal. I do not know whether edema is a descriptor similar to whitish turbidity, but most of the descriptions (Table 2) are of red ones.

What are the histological findings of minimal changes?

Abnormal endoscopic findings can be confirmed by histologic studies. Ismail-Beige and colleagues^{21,22} focused on the lengthening of the papillae and hyperplasia of the basal zone, which have been confirmed by other studies. In a recent report from Japan, similar histologic findings were reported to be identified in mucosa that had not been stained by Lugol spray,²³ suggesting that such changes are characteristic of acid-injured mucosa. In contrast, some reports claim that such findings are not found in nonerosive reflux disease,^{24–26} or that

they are not specific enough to determine acid-injured esophagus.²⁷ Takubo et al.²⁷ also suggested that histologically red ones show dilation of multiple intrapapillary vessels, while white ones show acanthosis with or without keratinization of the epithelium. They further showed that an acanthotic epithelium, a finding of “white ones,” has lost its normal basal cells, which is the opposite of hyperplasia of the basal zone. Does this mean that we see blood flow in the epithelium through dilated capillaries as “red ones” and obscured blood flow in acanthotic epithelium as “white ones?” If so, is it possible to say that “red ones” and “white ones” belong in the same category?

As in the gastric mucosa, a mild irritant may affect cellular function in the esophageal mucosa. In an experiment in rabbit, adaptive cytoprotection was shown in the esophageal mucosa,²⁸ but because no histological data were reported, we do not know what kind of histological changes are caused by mild irritants.

Is there any relation to nonerosive reflux disease or symptomatic GERD?

If minimal changes are definitely a result of acid reflux, should findings of minimal changes have any influence on the diagnosis or therapeutic decision making of nonerosive reflux disease (NERD) or symptomatic GERD (s-GERD)? If so, identification of minimal changes would be evidence for acid reflux in patients with reflux symptoms, and such patients would be identified as having NERD, but with minimal changes, or s-GERD with minimal changes. However, even among patients with minimal changes and reflux symptoms, some do not respond to proton pump inhibitors, because such subtle changes may not be responsible for the symptoms generated. Therefore, I believe that the identification of minimal changes in patients with reflux symptoms may not be useful for the detection of pathophysiology or for establishing therapeutic strategies, but this must be clarified.

What should we do about this issue?

Many Japanese endoscopists make the diagnosis of grade M reflux esophagitis because they identify reddish or whitish lesions. If we could describe the proper characteristics of minimal change, then not both red ones and white ones but just one of these categories could be considered grade M. Education with proper descriptive definitions could reduce interobserver variation significantly. Moreover, it is necessary to determine which findings, red ones or white ones, respond to acid

suppression pharmacotherapy or antireflux surgical therapy.

It is time to reevaluate the definition of minimal changes, their histology, pathophysiology, and symptomatology, and the appropriate pharmacological intervention.

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