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Minimal change oesophagitis: a disease with characteristic differences to erosive oesophagitis

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SUMMARY

Background: The majority of gastro-oesophageal reflux disease (GERD) seems to be non-erosive reflux disease. Nonerosive reflux disease includes minimal change oesophagitis (whitish or reddish, oedematous change and erosion that is not regarded as mucosal break) and no endoscopic abnormalities.

Aim: To investigate the accurate proportion of those with minimal change oesophagitis and to clarify its characteristics. In addition, we evaluated the effect of famotidine (40 mg/ day) in those with minimal change.

Methods: Prospective endoscopic assessment was performed for consecutive 606 out-patients. Of the 582 patients suitable for analysis, 347 were non-treated. The latter were divided into those with erosive GERD or

minimal change, and their endoscopic findings and characteristics were compared.

Results: Among 347 non-treated patients, 88 (25%) had erosive GERD and 249 (72%) had minimal change. Compared with patients who have erosive GERD and those with minimal change, the latter were less likely to have hiatal hernia or bile reflux, but more likely to have gastric atrophy. Symptomatic patients (n = 55) with minimal change oesophagitis were more likely to have hiatal hernia than those who were asymptomatic (n = 194). Most patients preferred taking famotidine on-demand, during a 4-week follow-up period.

Conclusions: Most non-erosive reflux disease can be classified as minimal change oesophagitis, and that have different characteristics from erosive GERD. On-demand famotidine may be a suitable alternative treatment for patients with minimal change disease.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus.¹ It includes a heterogeneous group of patients with differences in perception of pain, sensitivity to acid exposure and physiological tissue involvement. GERD is less common and milder in endoscopic severity in Asia than

in the West.² Endoscopy (oesophagogastrroduodenoscopy, EGD) is the gold standard for the diagnosis of erosive GERD and the Los Angeles (LA) classification of oesophagitis³ is generally accepted as the endoscopic assessment of GERD.

In Japan, the prevalence of erosive GERD (LA classification grades A, B, C and D) was <16.4% and most of these cases were grade A or B.^{4–7} The majority of GERD seems to be non-erosive reflux disease (NERD), especially in Japan. NERD includes minimal change oesophagitis (whitish or reddish, oedematous change and erosion that is not regarded as mucosal break) and no endoscopic abnormalities. Hoshihara reported that a

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minimal change, which did not have mucosal break, but was histologically reflux oesophagitis, was observed. Therefore, he proposed a modified LA classification of which includes the minimal change as grade M, and the oesophagus without any minimal change and mucosal break as grade N.⁷

Proton-pump inhibitors (PPIs) are generally the preferred drug in treatment of more severe form of erosive GERD;⁸ however, they are occasionally not effective for patients suffering from minimal change oesophagitis or NERD. This raises the question as to whether there are any different characteristics in erosive GERD and minimal oesophagitis or NERD.

The purpose of this prospective study is to investigate the accurate proportion of minimal change oesophagitis in Japanese patients by EGD and to clarify its characteristics. In addition, we evaluated the effect of 4 weeks of famotidine (40 mg/day) for the non-treated minimal change oesophagitis to survey patients after medication.

MATERIALS AND METHODS

Patients

Between August 2003 and July 2004, 606 consecutive out-patients who visited or were referred to the Masuyama Gastrointestinal Clinic for routine check-up, screening or further examination of malignancy because abnormal findings were detected in other hospitals. They underwent EGD by expert endoscopists. Informed consent was obtained from all patients.

Characteristics and reflux symptoms

Patient characteristics (gender, age, weight and height) and use of acid-suppressive drug or other medications for the stomach was collected and body mass index (BMI) of each patient was calculated. To diagnose GERD by reflux symptoms, a Japanese translation of the Carlsson-Dent questionnaire⁹ was completed by all patients, with the assistance of co-medical staff in instances where patients had difficulty completing it themselves. Patients scoring more than 4-points on the questionnaire were regarded as symptomatic GERD.

Endoscopic assessment

The EGD using video endoscope (Q-240, Olympus, Tokyo, Japan) was performed under conscious sedation

(diazepam 5–10 mg/patient), and examination time ranged from 10 to 20 min (in case of biopsy) per patient. Findings (60–100 pictures/patient) were documented by a digital filing system (Nexus, Tokyo, Japan) and digital video recordings (Sony, Tokyo, Japan). The presence or absence of columnar-lined epithelium (CLE) in the lower portion of oesophagus, reflux oesophagitis, hiatus hernia (HH), atrophic gastritis and the colour of gastric juice were examined by two expert endoscopists (TN and KS) without knowledge of results of the questionnaire. The final findings of reflux oesophagitis, HH, atrophic gastritis and bile reflux (by colour of gastric juice) were determined by two expert endoscopists after discussion and review of the findings.

Reflux oesophagitis

Reflux oesophagitis (erosive GERD) was graded according to LA classification³ and minimal change oesophagitis (grade M by Hoshihara⁷) was determined by the appearance of distal end of oesophageal mucosa (whitish or reddish colours, oedematous change and erosion that is not regarded as mucosal break). Patients without any minimal change appearances and mucosal break in their oesophagus were regarded as normal endoscopic findings.

Hiatus hernia

The distance between the incisor teeth and the oesophago-gastric (EG)-junction was recorded. HH was presently considered if gastric folds were assessed as extending more than 2 cm above the diaphragmatic hiatus during quiet respiration.¹⁰ To assess the association between HH and GERD, HH was divided into two grades: negative (none to <2 cm) and positive (more than 2 cm).

Atrophic gastritis

Severity of atrophic gastritis was assessed by EGD according to the atrophic pattern system by Kimura and Takemoto.¹¹ Atrophic gastritis was divided into seven types (C-0, C-1, C-2, C-3, O-1, O-2, O-3) based on the location of the atrophic border detected by EGD. To assess the association between atrophic gastritis and GERD, atrophic gastritis was divided into two types: closed-type (C-0, C-1, C-2, C-3; none-to-mild severity of

atrophy) and open-type (O-1, O-2, O-3: moderate-to-severe atrophy).

Bile reflux

To detect bile reflux in the stomach, gastric juice colour was observed and recorded as transparent, whitish, slightly yellowish, dark yellow and others (foods, bloody, etc.). Yellowish colour of gastric juice was regarded as bile reflux to the stomach, therefore, colour of the gastric juice was divided into two types: whitish (including transparent) and yellowish (non-transparent and whitish).

Statistical analysis

STATVIEW J-5.0 (SAS Institute, Tokyo, Japan) was used for statistical analysis. In comparison between minimal change oesophagitis and erosive GERD, an analysis of the proportion of HH, atrophic gastritis, bile reflux and reflux symptoms was carried out using the chi-square test and differences in ages and BMI was tested by Student's *t*-test. In comparison between symptomatic and asymptomatic minimal change oesophagitis, analysis of the proportion of HH, atrophic gastritis and bile reflux was carried out using the chi-square test, and differences of ages and BMI were tested by Student's *t*-test. *P*-values of <0.05 were considered to be significant.

Effect of famotidine for minimal change oesophagitis

Just after endoscopic assessment and the grading of reflux oesophagitis, patients with minimal change oesophagitis and mild erosive GERD (LA grade A with slight mucosal break) were randomly selected by the endoscopist. Regardless of the presence or absence of reflux symptoms, famotidine (40 mg/day) was prescribed to patients who were accepted with informed consent. After 4 weeks follow-up, the validated questionnaires shown in Table 1 were performed for these patients.

RESULTS

Patients' profiles and proportion of minimal change oesophagitis

Among 606 patients, 18 with resected stomach, four with advanced gastric cancer and two overlap cases were excluded. In 582 patients (307 male, 275 female, mean

Table 1. Validated questionnaires for the minimal change oesophagitis patients after medication

Symptoms (heartburn, regurgitation, chest pain, etc.)
Getting worse
No change
Disappeared or improved*
No symptom before medication
Famotidine
I want to take it every day
I want to take it on-demand
No need it because symptom(s) disappeared completely
Not effective

*Disappeared, disappeared every symptom completely; improved, improved or disappeared some symptom.

age: 54–56 years; age range: 18–94), 235 (40.4%) were taking medication [PPI 48, histamine₂-receptor antagonist (H₂RA) 116, mucoprotective substances 20, other medication 51], and the other 347 (59.6%) were not being medically treated for at least 4 weeks. In 582 patients, 146 (25.1%) were erosive GERD (LA grade A 119, B 14, C 13, D 0), 422 (72.5%) were minimal change oesophagitis (grade M), and 14 (2.4%) were normal endoscopic findings. In non-treated 347 patients (183 men, 164 women, mean age 53.12 years; age range: 18–94), 88 (25.4%) were erosive GERD (LA grade 71, B 10, C 7), 249 (71.8%) were minimal change oesophagitis (grade M) and 10 (2.8%) had normal findings. Two of 10 patients with endoscopic normal findings were symptomatic; thus they were regarded as grade N in the modified LA classification.⁷ Although CLE was observed in most patients, assessment of Barrett's oesophagus was not done in this study because biopsy from CLE was not performed.

Typical endoscopic pictures of non-treated patients were shown in Figures 1–5.

Comparison of erosive GERD and minimal change oesophagitis

Between minimal change oesophagitis (*n* = 249) and erosive GERD (*n* = 88) in non-treated patients, association of characteristics including final endoscopic findings were compared (Table 2).

Comparison of symptomatic and asymptomatic patients with minimal change oesophagitis

Between symptomatic (*n* = 55) and asymptomatic (*n* = 194) in patients with minimal change oesophagi-

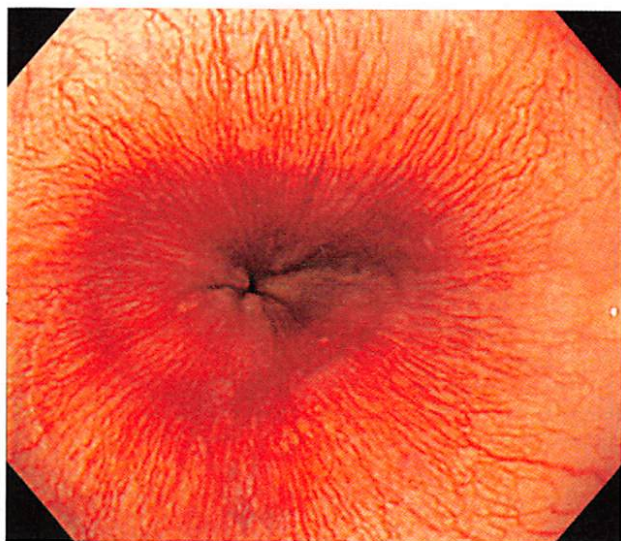


Figure 1. No endoscopic abnormalities (asymptomatic). No whitish change in squamo-columnar (sc)-junction and no hiatal hernia.

tis, the association of characteristics including final endoscopic findings were compared (Table 3).

Follow-up after 4 weeks of famotidine

Among 40 minimal change oesophagitis and 20 mild erosive GERD (LA grade A with slight mucosal break) in

non-treated patients, 15 and seven patients respectively completed the validated questionnaires (Table 1) after a 4-week follow-up period of taking famotidine (40 mg/day). The characteristics, endoscopic findings of 22 patients and the results of questionnaires were listed in Table 4.

DISCUSSION

In Japan, EGD is a popular examination for the screening and further examination of upper gastrointestinal (GI) to diagnosis gastritis, ulcers and tumours such as gastric cancer. In this study, we found 20 cases of tumours (15 gastric adenomas and early gastric cancer, one early oesophageal cancer, four advanced gastric cancer). Most of these cases were successfully treated by surgery or endoscopically. Observation of EG-junction to assess GERD was not the major aim because the main purpose of EGD is locating tumours, particularly in the stomach, until quite recently. Moreover, GERD has been regarded as less common and milder in endoscopic severity in Asia including Japan than in the West.^{2, 4-7}

For endoscopic assessment of GERD in Japanese patients, LA classification seemed to be insufficient; therefore, modified LA classification⁷ was applied in this study. To diagnose minimal change oesophagitis,

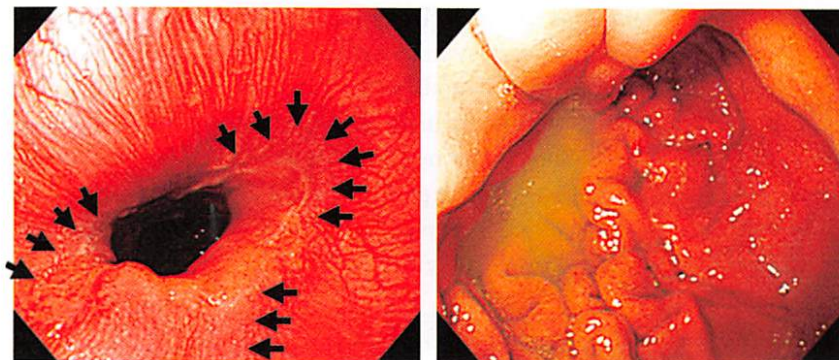


Figure 2. Minimal change oesophagitis (symptomatic). Left, whitish change (arrows showing) in sc-junction; right, yellowish colour of gastric juice.

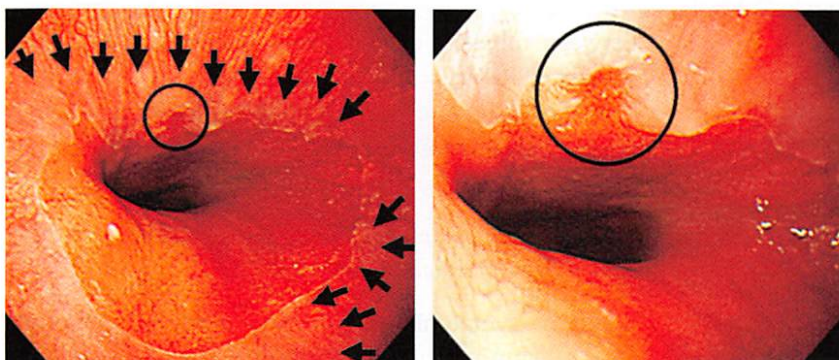


Figure 3. Los Angeles (LA) grade A (asymptomatic). Left, whitish change (arrows showing) in sc-junction; right, mucosal break (circled) <5 mm.

Figure 4. Los Angeles (LA) grade B (asymptomatic). Left, mucosal break more than 5 mm; right, hiatal hernia and mucosal break.

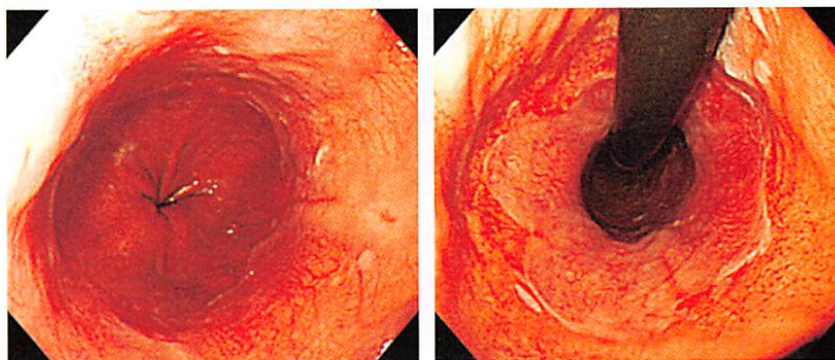


Figure 5. Los Angeles (LA) grade C (asymptomatic). Left, mucosal break is continuous; right, hiatal hernia and mucosal break.

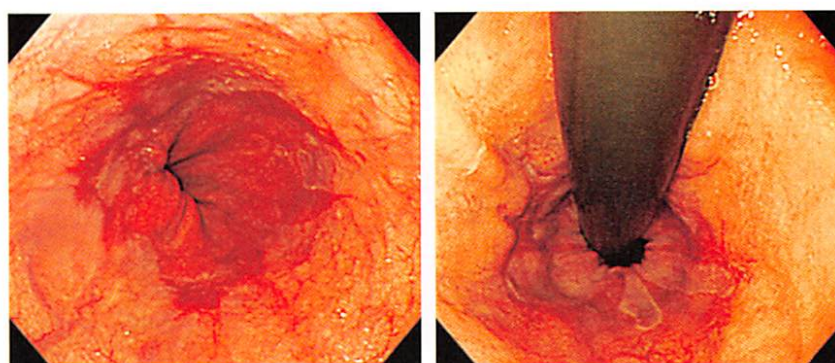


Table 2. Comparison of minimal change oesophagitis and erosive GERD

	Minimal change	Erosive GERD	P-value
Number of patients	249	88	
Age (years)	53.27	52.79	N.S.
Gender (male/female)	126/123	57/31	0.0218
HH (positive/negative)	56/193	37/51	0.00042
Atrophy (open/closed)	107/142	22/66	0.00286
Bile (positive/negative)	86/163	43/45	0.0175
Symptom (≥ 4 / < 4)	55/194	20/68	N.S.
BMI	23.089	23.333	N.S.

GERD, gastro-oesophageal reflux disease; HH, hiatus hernia; BMI, body mass index.

Table 3. Comparison of symptomatic and asymptomatic patients

	Symptomatic	Asymptomatic	P-value
Number of patients	55	194	
Age (years)	52.22	53.58	N.S.
Gender (male/female)	24/31	102/92	N.S.
HH (positive/negative)	18/37	38/156	0.0394
Atrophy (open/closed)	19/36	88/106	N.S.
Bile (positive/negative)	25/30	61/133	N.S.
BMI	22.727	23.311	N.S.

HH, hiatus hernia; BMI, body mass index.

Hoshihara⁷ emphasized the importance of endoscopic observation of longitudinal vascular structures located in distal portion of oesophagus; namely, the palisade zone, composed of parallel vessels arranged in groups, lying mainly within the lamina propria.¹² Usually, it is difficult to correctly observe the distal portion of oesophagus, because of patient's discomfort and the oesophageal wall's movement because of the heartbeat and breathing exercises.

After endoscopic assessment under conscious sedation by expert endoscopists, 88 (25.4%) were diagnosed as erosive GERD (LA grade 71, B 10, C 7), 249 (71.7%) as minimal change oesophagitis (grade M), two (0.6%) as grade N (normal findings by EGD but symptomatic) and eight (2.3%) as normal (normal findings by EGD and asymptomatic) among non-treated 347 patients. The proportion of erosive GERD was higher than formerly reported, but most cases were mild (LA grade A, B). Surprisingly, the proportion of minimal change oesophagitis (grade M) was over 70% of 347 non-treated patients. Recently, many gastroenterologists are increasingly interested in the issue of NERD. At this time, NERD is regarded as non-endoscopic abnormality or minimal change oesophagitis. In our study, two patients of grade N and 249 patients of grade M (minimal change

Table 4. Follow-up after 4 weeks of famotidine

Age	Gender	HH	Atrophy	Gastric juice	Score*	Symptom	Famotidine
Asymptomatic minimal change oesophagitis (score*: <4)							
41	M	Negative	None (C-0)	Yellowish	0	Disappeared	On-demand
55	F	Negative	None (C-0)	Whitish	0	Disappeared	On-demand
34	F	Negative	Closed	Whitish	1	Disappeared	On-demand
Symptomatic minimal change oesophagitis							
62	F	None	Closed	Yellowish	4	Disappeared	On-demand
66	F	Negative	Open	Yellowish	4	Improved	On-demand
55	F	Positive	Open	Whitish	5	Disappeared	Daily
65	M	Negative	Open	Whitish	5	No change	No effect
66	F	Positive	Open	Whitish	6	Improved	On-demand
45	M	Negative	Open	Whitish	8	–	On-demand
52	M	Negative	Closed	Yellowish	8	Disappeared	On-demand
34	F	Negative	Closed	Yellowish	8	Improved	On-demand
46	M	Negative	Open	Yellowish	9	Disappeared	On-demand
51	F	Negative	Open	Whitish	9	Improved	On-demand
55	F	Negative	Open	Whitish	9	Disappeared	Daily
48	F	Negative	Open	Whitish	11	No change	Daily
Mild erosive GERD (LA grade A)							
47	M	Positive	Closed	Yellowish	0	Improved	No need
56	F	Negative	Closed	Yellowish	0	–	No need
78	M	Positive	Closed	Whitish	0	Improved	On-demand
73	F	Positive	None (C-0)	Whitish	1	Disappeared	On-demand
63	M	Negative	Open	Whitish	6	Disappeared	On-demand
47	M	Negative	Closed	Whitish	8	No change	On-demand
56	F	Negative	Closed	Yellowish	11	Disappeared	On-demand

*By Carlsson-Dent questionnaire before medication.

LA, Los Angeles; HH, hiatus hernia; GERD, gastro-oesophageal reflux disease.

oesophagitis) were considered to be NERD (72.3% in non-treated patients). Indeed, the combination of high resolution magnifying endoscopy and histological markers leads to predict minimal change oesophagitis;¹³ however, minimal change oesophagitis can be observed by an adequate method of EGD.

Before establishment of LA classification, endoscopists in Western countries discussed minimal change oesophagitis.¹⁴ At that time, agreement between inexperienced endoscopists was poor for the recognition of minimal changes, but was good for the recognition of mucosal breaks. Therefore, they did not take account of minimal change oesophagitis in LA classification. Recently, the flexible endoscope was changed from fiberscope to video endoscope, and its resolution is becoming increasingly higher than before. Moreover, endoscopic diagnosis of NERD including minimal change oesophagitis seems to be gradually increasing in importance. Thus, new classification of oesophagitis including minimal change has become necessary at this juncture. The modified LA classifica-

tion by Hoshihara⁷ has the potential to be one proposed method.

From the results of our study, minimal change oesophagitis seems to occur with roughly the same frequency in men as in women. On the contrary, erosive GERD seemed to be more common in men than women. Compared with patients who have erosive GERD ($n = 88$), those with minimal change oesophagitis ($n = 249$) are likely to be less with HH and bile reflux and more with atrophy of stomach. There was no significant difference in age, symptoms and BMI between minimal change oesophagitis and erosive GERD (Table 2).

Fifty-five (22.1%) of 249 non-treated patients with minimal change oesophagitis were symptomatic. Compared with asymptomatic patients ($n = 194$), symptomatic patients ($n = 55$) are likely to be more with HH (Table 3).

These findings are consistent with the latest report that the presence of HH correlates with more severe endoscopy findings, and predisposes severe histological abnormality in cases of NERD.¹⁵ The HH has been

considered one incidental finding of little consequence by reflux oesophagitis. Recently, many investigators report that HH contributes oesophageal mucosal injury, particularly in patients with severe erosive GERD.¹⁶

Studies using ambulatory pH and oesophageal bile reflux monitoring (Bilitec, Medtronic Inc., Skovlunde, Denmark) have shown that not only acid reflux but also duodenogastro-oesophageal reflux frequently occurs in patients with GERD whose response to single-dose PPI is poor.¹⁷ Ambulatory pH and Bilitec monitoring seems to be the best examination to assess duodenogastro-oesophageal reflux; however, it requires 24-h and may cause discomfort in patients. Usually, bile reflux to the stomach makes colour change of gastric juice from transparent (or white) to yellowish. In our results, a yellowish colour of gastric juice (that may be indicating bile reflux) was more common in patients with erosive GERD than in those with minimal change oesophagitis. Yellowish colour of gastric juice may be a simple indicator of bile reflux.

Helicobacter pylori infection in the stomach affects atrophic change and gastric acid secretion; subsequently it has been thought to be related to the severity of GERD. Recently, Fallone *et al.* reported that there is no difference in disease severity of GERD between patients infected and not infected with *H. pylori*.¹⁸ On the contrary, Haruma *et al.* reported that age-correlated decrease of gastric acid secretion in *H. pylori*-positive subjects depended on an increasing prevalence of fundic atrophic gastritis with age.¹⁹ In this study, *H. pylori* infection in the stomach was not examined, but the severity of gastric atrophy was assessed endoscopically. Closed-type atrophic gastritis (C-0, C-1, C-2, C-3) is non-atrophic to mild-severity atrophy; open-type atrophic gastritis (O-1, O-2, O-3) is moderate-to-severe atrophy. Closed-type atrophic gastritis is located generally smaller in the fundic gland mucosa than open-type. Therefore, depression of gastric acid secretion is supposed to be less in the closed type as opposed to open-type. Concerning the severity of atrophic gastritis, patients with minimal change oesophagitis were more likely to be open-type than those with erosive GERD. This result of our study may be understandable.

Concerning pharmacological management of GERD, PPI should be the preferred drug in the treatment of severe-form erosive GERD, and H₂RA should be considered for sporadic or mild GERD.⁸ PPI should be the drug of choice even for healing lower grade reflux oesophagitis, especially in *H. pylori*-negative patients and treat-

ment with H₂RA may be an alternative choice in *H. pylori*-positive patients.²⁰ According to a recent meta-analysis review, PPI is superior to H₂RA for short-term relief of heartburn in patients with NERD, but the difference of efficacy is not so remarkable.²¹ In this study, the initial plan was to compare the efficacy of famotidine for minimal change oesophagitis and that for mild erosive GERD by original questionnaires. Unfortunately, few patients completed the questionnaires. Therefore, the characteristics, endoscopic findings of 22 patients, and the results of questionnaires were listed in Table 4. From the results, most of the patients answered that their symptoms improved or disappeared completely and they indicated a desire to take famotidine in case of need. Further investigation may be required, however, as to whether prescribing famotidine on-demand is an appropriate treatment for patients with mild oesophagitis.

In conclusion, most of NERD can be classified as minimal change oesophagitis: it has different characteristics from erosive GERD; less instances HH, closed type atrophy of the stomach and bile reflux than the latter. Among minimal change oesophagitis, symptomatic patients are likely to have a higher prevalence of HH than asymptomatic patients. On-demand taking of famotidine may be one possible treatment for patients with mild oesophagitis. To diagnose both erosive GERD and minimal change oesophagitis, correct endoscopic assessment is required.

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