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Evaluation of Gastroesophageal Reflux and Gastroesophageal Reflux Disease with Esophageal Endoscopy and Histology in Children

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SUMMARY

Objectives : The roles of esophageal endoscopy and mucosal biopsy in making diagnoses of gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) were retrospectively examined in children.

Methods : Thirty-four patients, whose ages ranged from 1 month to 18 years (median, 4 years), underwent diagnostic evaluation of GER/GERD. Group I patients (n=5) had symptoms suggesting GER, but had no underlying abnormalities. Group II patients (n=23) had chronic symptoms suggesting GERD and underlying abnormalities, neurologic impairment (n=22) and post-repair of esophageal atresia (n=1). Group III patients (n=6) were neurologically impaired but had no symptoms and underwent evaluation as a preoperative examination of gastrostomy placement. Reflux esophagitis was endoscopically graded according to the modified Los Angeles classification and grouped into grades \leq M, A, and \geq B. The results of GER studies and the histologic findings of reflux esophagitis were compared between these groups.

Results : The parameters of 24-h pH monitoring were significantly higher in patients with grade \geq B than grade \leq M, and endoscopic grades improved after antireflux surgery along with the improvements in reflux index. There were no significant correlations between the endoscopic grade and the percentages of patients in whom histologic findings of reflux esophagitis were present.

Conclusion : Esophageal endoscopy is useful for examining the severity of reflux esophagitis and monitoring the effect of treatment in children with GER/GERD. The modified Los Angeles classification can also be used for that purpose. Although treatment is seldom influenced by the results, histologic evaluation of the esophageal mucosa should be performed to exclude other disorders.

Key Words : gastroesophageal reflux (GER), gastroesophageal reflux disease (GERD), endoscopy, esophageal histology

INTRODUCTION

Gastroesophageal reflux (GER) is common in infants, and physiologic GER resolves spontaneously as a result of functional maturation. In contrast, non-physiologic GER develops in neurologically impaired children as well as children with congenital malformations^{1~4)}.

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Table 1 Characteristics of 34 patients who underwent GER/GERD evaluation

Patient group	n	Age	Gender (M/F)	Underlying abnormality	Symptoms suggesting GER/GERD
I	5	1 month - 11 months (2 months)*	5/0	None	Milk vomiting (n=4), cyanotic spells after milk feeding (n=1)
II	23	4 months - 18 years (9 years)	16/7	Neurologically impaired (n=22), post-surgical repairs of EA and CES (n=1)	Vomiting, hematemesis, dysphagia, or respiratory symptoms such as recurrent pneumonia, stridor, desaturation during feedings, and asthma
III	6	1 year - 12 years (2 years)	1/5	Neurologically impaired, gastrostomy to be placed for nutrition	None

* Range (median)

Abbreviations : GER : gastroesophageal reflux, GERD : gastroesophageal reflux disease, EA : esophageal atresia, CES : congenital esophageal stenosis

Pathologic GER causes gastroesophageal reflux disease (GERD) that includes respiratory problems, reflux esophagitis, malnutrition and growth retardation.

A comprehensive investigation with contrast study, 24-hour pH monitoring, and esophageal endoscopy is necessary in patients with suspected GERD according to the guidelines for the evaluation and treatment of childhood GER⁵⁻⁹. However, particularly in children with neurologic impairment or those with congenital malformations, the presence of GER and its causal relationships with symptoms cannot always be defined with these diagnostic tests.

Esophageal endoscopy is able to determine the presence of reflux esophagitis, stricture and Barrett's esophagus, while excluding other disorders^{10,11}. The endoscopic findings of reflux esophagitis are classified according to grading systems¹². Mucosal biopsies are taken to confirm histologically the presence of esophagitis, fibrotic stricture, or epithelial Barrett's metaplasia. The grading systems, however, have not been validated in children, and there are controversies regarding the usefulness of a histologic examination in pediatric patients¹³. Esophageal endoscopy in children usually necessitates general anesthesia or sedation ; therefore, the benefits of endoscopy must be weighed against the minimal, but not negligible, those risks, and the advantages and disadvantages of the examination should be clarified. In this study, to clarify the roles of these diagnostic tests in children with GER and GERD, the results of esophageal endoscopy and mucosal biop-

sies were retrospectively examined.

MATERIALS AND METHODS

Patients

Between August 2007 and February 2011, 34 patients underwent diagnostic evaluation of GER and GER-related symptoms or complications (GERD). The ages of the patients, 22 male patients and 12 female patients, ranged from 1 month to 18 years (median, 4 years). Twenty-eight of the 34 patients were neurologically impaired due to disorders such as cerebral palsy, chromosomal abnormalities, multiple congenital anomalies, and acquired encephalitis. The patients were categorized into 3 groups (Table 1). Group I patients (n=5) had symptoms suggesting the presence of GER, but had no underlying abnormalities. The ages of the patients ranged from 1 month to 11 months (median, 2 months), and symptoms were milk vomiting in 4 patients and cyanotic spells after milk feeding in 1 patient. Group II patients (n=23) had chronic symptoms suggesting GERD and had underlying abnormalities. The ages ranged from 4 months to 18 years (median, 9 years), and symptoms were vomiting, hematemesis, dysphagia, or respiratory problems such as recurrent pneumonia, stridor, desaturation during feedings, and asthma. There were 22 patients with neurologic impairment and 1 patient who had undergone repairs of the esophageal atresia and had congenital esophageal stenosis. Group III patients (n=6) were neurologically impaired but had no symptoms suggest-

ing GER. They underwent GER evaluation as a preoperative examination of gastrostomy placement for nutritional support. The ages ranged from 1 year to 12 years (median, 2 years).

GER/GERD evaluation

The GER/GERD evaluation included a contrast study, 24-h pH monitoring, and esophageal endoscopy. Esophageal endoscopy and pH monitoring were performed in all patients, and the contrast study was performed in 33 patients.

For contrast study of the esophagus and the stomach, an almost equal amount of barium or nonionic contrast medium to normal meal was introduced to the esophagus. The stomach was then adequately distended with a contrast agent and air since an insufficiently distended stomach can reduce reflux episodes.

Esophagogastric pH monitoring was performed to detect acid reflux within the esophagus and to measure the frequency and duration of reflux events over a 24-h period using a Medtronic Digitrapper™ pH 400 (Asahi Biomed, Co., Tokyo, Japan). Monitoring was performed essentially according to the guidelines of the Japanese Society for Pediatric Neurogastroenterology⁶⁾. Medications that alter gastric pH, such as histamine H₂-receptor antagonists and proton pump inhibitors, were stopped at least 72 h before the study. A two-channel pH probe was introduced to simultaneously monitor esophageal and gastric pH profiles. The monitoring condition was unrestricted and daily habits were allowed to replicate the patient symptoms. Meals, body position, and sleeping/awaking were recorded. The results of pH monitoring were interpreted by reflux index, reflux episodes (the number of refluxes in 24 h), long reflux episodes (the number of refluxes continuing more than 5 min in 24 h), and duration of the longest reflux, all of which were automatically calculated by the Polygram 98 Diagnostic Workstation software for the Digitrapper™ pH 400. The reflux index reflects esophageal acid exposure time and was defined as the percentage of time during which pH was less than 4.0 in the esophagus. The normal limit of the reflux index was set at 4.0%, according to the 95th percentile value in normal children. It was thought that symptoms were associated with reflux events when their timings were very close or the symptom index¹⁴⁾ was high, and the

correlation as well as the reflux index was taken into account when GERD was diagnosed.

Esophageal endoscopy

Esophageal endoscopy was performed to evaluate reflux esophagitis and examine other abnormalities. Endoscopic visualization of reflux esophagitis was in the form of mucosal breaks (erosion and ulceration), and was graded according to the modified Los Angeles (LA) classification¹²⁾. Briefly, grade N is a normal finding, grade M : minimal changes, grade A : one or more mucosal breaks (each no longer than 5 mm) confined to one mucosal fold, grade B : at least one mucosal break more than 5 mm in length, but mucosal breaks are confined to one mucosal fold and not continuous between the tops of two mucosal folds, grade C : at least one mucosal break is continuous between the tops of two or more mucosal folds but not circumferential, and grade D : circumferential mucosal breaks. A stricture due to reflux esophagitis appears as a white annular infundibular narrowing with a central lumen surrounded by actively inflamed or pale mucosa. Hiatal hernia can be recognized by locating the diaphragmatic ring and the Z-line.

Histologic evaluation of reflux esophagitis

For the histologic evaluation of reflux esophagitis, mucosal specimens were taken by grasp biopsy from the most damaged parts of the esophagus. Esophageal mucosa 1 cm above the esophagogastric junction was also taken. Histologic findings were classified into normal, esophagitis, scar formation, and mucosal columnar metaplasia (Barrett esophagus). The presence of esophagitis was suggested when papillary elongation (papillae reaching into the upper-third of the epithelium) or intraepithelial inflammatory cell infiltration were observed. Basal zone hyperplasia was not included in the criteria of reflux esophagitis in this study since it was sometimes difficult to objectively evaluate the thickness of the basal zone of squamous epithelium. The numbers of infiltrating cells and eosinophils were counted and considered significant when the count was more than 20 in a high-power field (HPF).

Laparoscopic Nissen fundoplication

Laparoscopic Nissen fundoplication was a routine

Table 2 Management and outcome of patients based on GER/GERD evaluation

Patient group	n	Contrast study		Reflux index	Endoscopic grades of reflux esophagitis	Histologic diagnosis (normal/esophagitis)	Treatment	Follow-up	Outcome
		GER	Hiatal hernia						
I	5	4 (80)*	2 (40)	5.2 - 25.2 (6.4)**	N/M (n=5)	1/3	Conservative	11 months - 36 months (28 months)	All symptom-free
II	23	20 (87)	13 (57)	0 - 56.2 (14.9)	N/M (n=7) A (n=7) B/D (n=9)	0/20***	Fundoplication (n=18) Tracheostomy (n=1) Conservative (n=4)	0.5 month - 53 months (31 months)	Alive (n=20) Dead (n=3)
III	6	4 (67)	1 (17)	0.3 - 9.0 (1.7)	N/M (n=4) A (n=2)	0/2	Gastrostomy (n=5) Gastrostomy with fundoplication (n=1)	1 month - 54 months (39 months)	All alive without additional surgery

* Numbers in parentheses indicate percentages of patients.

** Range (median)

*** Scar formation and Barrett esophagus were diagnosed in 2 patients and 1 patient, respectively.

procedure performed as antireflux surgery. It was indicated in patients with GERD that could not be managed with medical treatments. It was also indicated when the presence of GER was confirmed by the pre-gastrostomy work-up studies. Under laparoscopic view, the procedure was started by dividing the gastrohepatic ligament, leaving the hepatic branches of the vagal nerve intact. The distal esophagus was dissected, taking care not to injure the vagal nerves, and mobilized to secure 3 to 4 cm of intra-abdominal esophagus. The diaphragmatic crura were approximated by stitches with non-absorbable sutures. A gap, into which an instrument of 5 mm in diameter could be inserted, was left between the wall of the esophagus and the inner rim of the diaphragmatic crus. The gastric fundus was then mobilized with 1 or 2 short gastric vessels divided, and a tension-free wrap was made by covering the intra-abdominal segment of the esophagus with the anterior and posterior walls of the gastric fundus. Approximation of the fundus was accomplished by 3 or 4 interrupted stitches with non-absorbable sutures, and 1 or 2 of the stitches incorporated the anterior wall of the esophagus. Finally, fundoplication was approximately 2 or 3 cm in length. In addition, gastrostomy was performed when feeding problems were present and pyloroplasty was added in patients with delayed gastric emptying.

Statistical analyses

The endoscopic grades of reflux esophagitis according to the modified LA classification were grouped into three groups: less than or equal to M ($\leq M$), A, and greater than or equal to B ($\geq B$). The results of GER studies and histologic findings of reflux esophagitis were compared between these groups. Mann-Whitney's U-test was applied when comparing continuous variables, and Fisher's exact probability test or the Chi-square test was applied to the categorical data. Statistical analysis was performed with SPSS 20 (SPSS Japan Inc., Tokyo, Japan) and p-values less than 0.05 were defined as significant. This study was reviewed and approved by the institutional review board of Dokkyo Medical University Koshigaya Hospital.

RESULTS

Management and outcome of patients based on GER/GERD evaluation

The results of GER/GERD evaluation, patient treatment, follow-up and the outcome are summarized in Table 2. In Group I, contrast study demonstrated GER in 4 patients who complained of vomiting. Small hiatal hernia was revealed in 2 patients. The reflux index was 25.2 in a patient with hiatal hernia, but ranged from 5.2 to 6.4 in the other 3 patients. In a patient with cyanotic spells after feeding, contrast study failed to

Table 3 Endoscopic grade of reflux esophagitis and results of contrast study and 24-h pH monitoring

	Endoscopic grade of reflux esophagitis			Total
	≤M	A §	≥B	
n	16	9	9	34
Contrast study				
GER	12 (75) ¶	8 (100)	8 (89)	28 (85)
Hiatal hernia	7 (44)	4 (50)	5 (56)	16 (48)
24-h pH monitoring				
Reflux index (% time < pH 4)	7.5 ± 1.8 #	14.4 ± 4.1	27.4 ± 6.4 *	14.6 ± 2.5
Reflux episodes in 24 h	139.3 ± 23.0	179.7 ± 37.7	235.1 ± 49.0	175.4 ± 20.1
Long reflux (>5 min) episodes in 24 h	3.7 ± 1.2	7.6 ± 2.0	17.9 ± 4.6 **	8.5 ± 1.7
Longest reflux (min)	19.8 ± 6.2	49.7 ± 26.0	47.8 ± 11.8 ***	35.1 ± 8.2

§ Contrast study was not performed in 1 patient.

¶ Numbers in parentheses indicate percentages of patients.

Mean ± SE

Asterisks indicate statistically significant differences when compared with grade ≤M. * p=0.007, ** p=0.004, *** p=0.043

demonstrate GER but the reflux index was 7.3. Endoscopic grade of reflux esophagitis was N or M in all patients in this group. Esophageal biopsy was performed in 4 patients, and histology was interpreted as normal in 1 patient and esophagitis in 3 patients. Based on these findings, patients were treated conservatively, followed-up for periods ranging from 11 months to 36 months (median, 28 months), and confirmed to be doing well with their symptoms resolving spontaneously.

In Group II, contrast study demonstrated GER in 20 patients and hiatal hernia in 13 of the 22 patients examined. The reflux index ranged from 0 to 56.2 (median, 14.9), and endoscopic grade was N or M in 7 patients, A in 7 patients, and B or D in 9 patients. Biopsy was performed in 20 patients, and mild or moderate esophagitis was histologically diagnosed in all these patients. Among the 9 patients with grade B or D esophagitis, scar formation was diagnosed in 2 patients and Barrett esophagus in 1 patient. Fundoplication was indicated in 19 patients and performed in 18 patients. One patient was treated conservatively because the parents refused surgical treatments. Gastrostomy was placed in 13 patients and pyloroplasty was added in 1 patient. Of the remaining 4 patients, 1 patient underwent tracheostomy due to severe aspiration and 3 patients with grade N or M esophagitis were treated conservatively. The patients were followed-up for periods ranging from 0.5 months to 53 months (median, 31 months). There were three major complications after

fundoplication : gastric volvulus, pyloric perforation, and GER recurrence due to wrap migration, all of which needed surgical treatment. At the end of the follow-up, 20 patients were alive and 3 patients were dead due to causes probably unrelated to GER, including necrotizing enterocolitis in 1 patient and sudden death in 2 patients.

In Group III, contrast study demonstrated GER in 4 patients and hiatal hernia in 1 patient. The reflux index ranged from 0.3 to 9.0 (median, 1.7), and endoscopic grade was N or M in 4 patients and A in 2 patients. Esophagitis was histologically diagnosed in 2 patients. While gastrostomy with fundoplication was indicated in 1 patient with grade A esophagitis and a reflux index of 9.0, gastrostomy without fundoplication was performed in the other 5 patients who were negative for GER. The patients were followed-up for periods ranging from 1 month to 54 months (median, 39 months), and all were alive without any additional surgery at their last follow-up.

Relationships between endoscopic grade of reflux esophagitis and the results of contrast study and 24-h pH monitoring

The relationships between endoscopic grade of reflux esophagitis and the results of contrast study and 24-h pH monitoring are summarized in Table 3. The endoscopic grade of reflux esophagitis was ≤M in 16 patients, A in 9 patients, and ≥B in 9 patients. Contrast

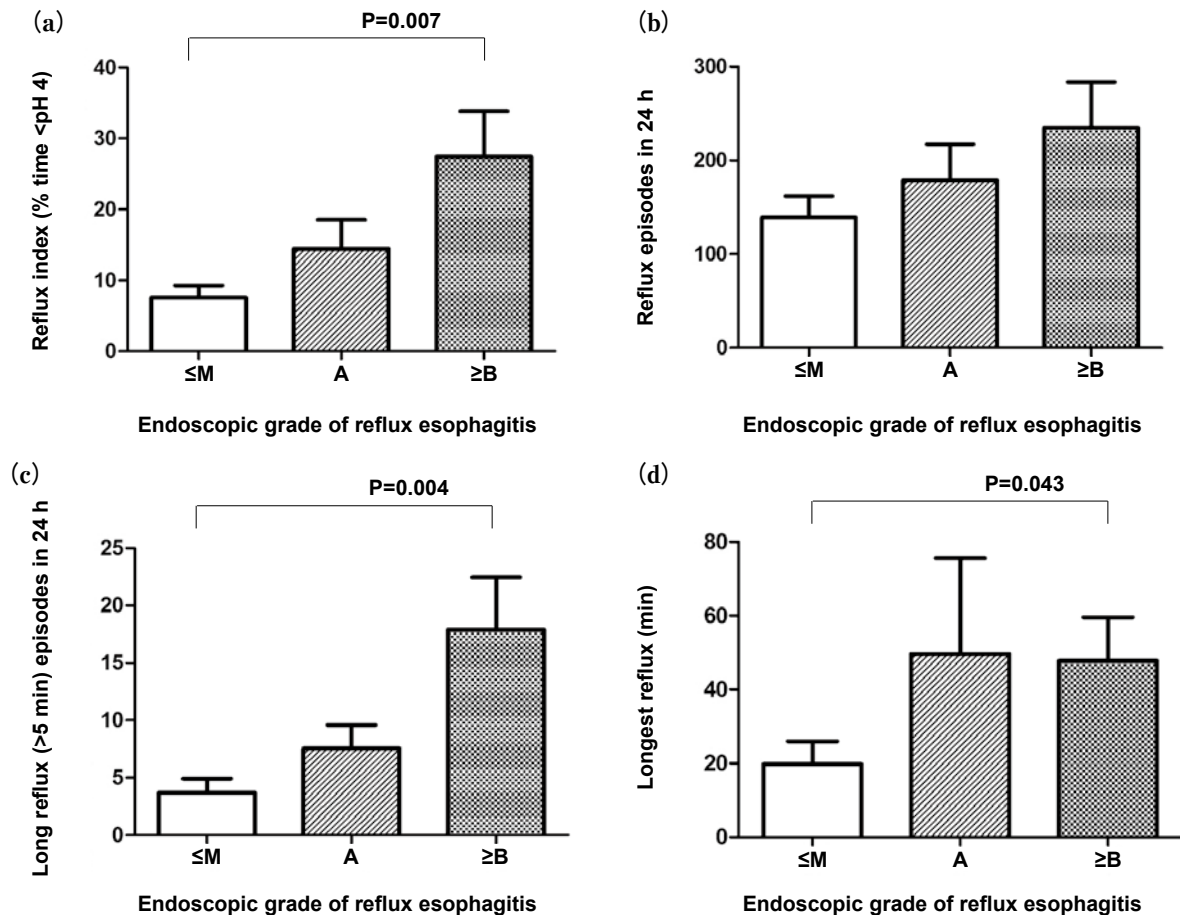


Fig. 1 (a) Endoscopic grades of reflux esophagitis and the reflux index, (b) the number of reflux episodes in 24 h, (c) the number of long reflux episodes (more than 5 min) in 24 h, and (d) the duration of the longest reflux. The reflux index, the number of long reflux episodes, and the duration of the longest reflux were significantly higher in patients with grade \geq B reflux esophagitis than in patients with grade \leq M. Columns with a bar indicate mean and standard error.

study demonstrated GER in 28 (85%) patients and hiatal hernia in 16 (48%) patients of the 33 patients examined. There were no significant correlations between the endoscopic grade of reflux esophagitis and the rate of GER demonstration or the percentage of patients with hiatal hernia.

The results of 24-h pH monitoring of the esophagus were compared between the endoscopic grades of reflux esophagitis. The reflux index, the number of reflux episodes in 24 h, the number of long reflux episodes (more than 5 minutes) in 24 h, and the duration of the longest reflux tended to be higher in patients with higher endoscopic grades. Of these, the reflux index, the number of long reflux episodes, and the duration of the longest reflux were significantly higher in patients with grade \geq B than in those with grade \leq M (Fig. 1a-

d).

Endoscopic grade and histologic findings of reflux esophagitis

The relationships between endoscopic grade and histologic findings of reflux esophagitis are shown in Table 4. Esophageal biopsy was performed in 26 patients excluding 5 patients with grade \leq M and 3 patients with grade A. Inflammatory cell infiltration (\geq 20/HPF) was observed in 5 (45%) patients with grade \leq M, 6 (100%) patients with grade A, and 6 (67%) patients with grade \geq B, while intraepithelial eosinophil infiltration was recognized in only 1 (9%) patient with grade \leq M and another 1 (17%) patient with grade A (Fig. 2.a). Papillary elongation was observed in 4 (36%) patients with grade \leq M, 3 (50%) patients with grade A, and 4

Table 4 Endoscopic grade and histologic findings of reflux esophagitis

Histologic findings	Endoscopic grade of reflux esophagitis			Total
	≤M	A	≥B	
n	11	6	9	26
Inflammatory cell infiltration (≥20/HPF)	5 (45) §	6 (100)	6 (67)	17 (65)
Eosinophil infiltration (≥20/HPF)	1 (9)	1 (17)	0	2 (8)
Papillary elongation	4 (36)	3 (50)	4 (44)	11 (42)
Scar formation	0	0	2 (22)	2 (8)
Barrett esophagus	0	0	1 (11)	1 (4)

§ Numbers in parentheses indicate percentages of patients.

Abbreviation : HPF ; high-power field

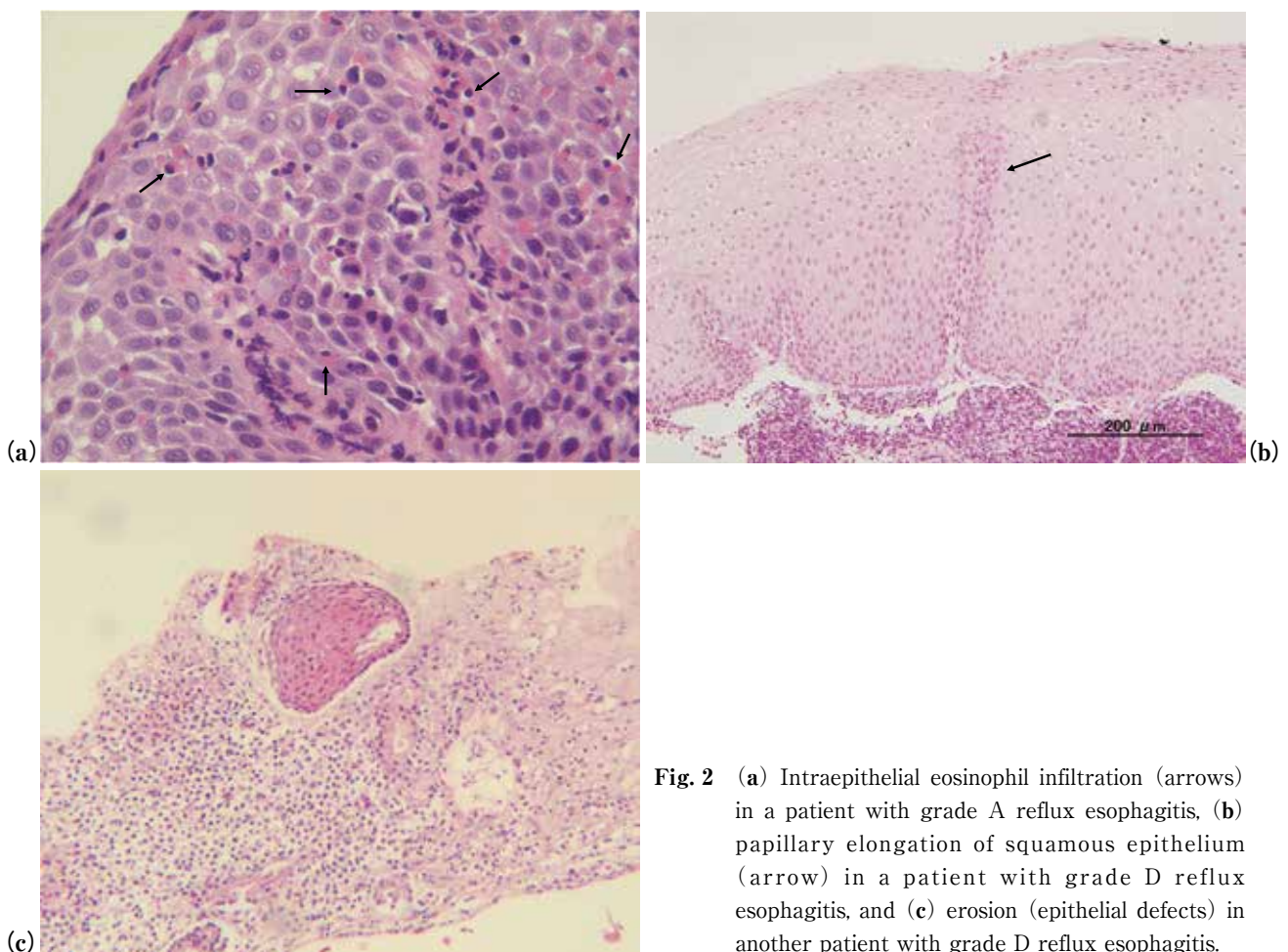


Fig. 2 (a) Intraepithelial eosinophil infiltration (arrows) in a patient with grade A reflux esophagitis, (b) papillary elongation of squamous epithelium (arrow) in a patient with grade D reflux esophagitis, and (c) erosion (epithelial defects) in another patient with grade D reflux esophagitis.

(44%) patients with grade \geq B (Fig. 2b, c). There were no significant correlations between the endoscopic grade of reflux esophagitis and the percentages of patients in whom these histologic findings were seen. Scar formation and Barrett esophagus were observed in patients with grade \geq B as described above and their incidences were 22% and 11% , respectively.

Esophageal endoscopy after fundoplication

Postoperative esophageal endoscopy was performed in 3 patients with grade D reflux esophagitis for whom an informed consent was obtained from the parents. The periods from fundoplication to examination ranged from 15 months to 34 months. Along with improvements in the level of reflux index, mucosal lesions of the esophagus were conspicuously restored and endo-

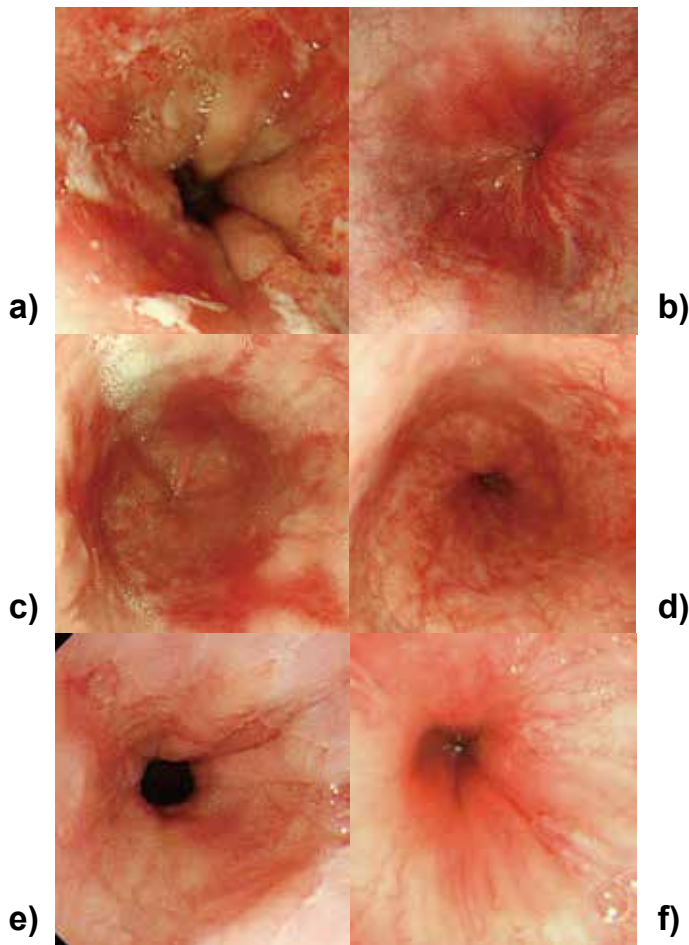


Fig. 3 Endoscopic appearance of the esophagus before and after antireflux surgery. Preoperative appearance of grade D reflux esophagitis (**a**) patient 1, (**c**) patient 2, and (**e**) patient 3. Postoperatively, the mucosal lesions were restored and the endoscopic grade was N or M (**b**) patient 1, (**d**) patient 2, and (**f**) patient 3.

scopic grade was classified into N or M postoperatively (Fig. 3).

DISCUSSION

GER in children causes diverse clinical symptoms. Physiologic GER causes milk regurgitation, vomiting or irritability in infants, but it can be managed conservatively with frequent feeding, thickening of feeds, or postural treatments. Pathologic GER in children, in contrast, causes complications including respiratory symptoms, reflux esophagitis, esophageal stricture, and consequent failure to thrive. Pathologic GER frequently develops in children with neurologic impairment as well as in children with congenital malformations¹⁻⁴. GER is a common problem occurring after repairs of esophageal atresia (tracheoesophageal fistula), diaphragmatic hernia, or abdominal wall defects.

Children with neurologic impairment have abnormalities of the central nervous system that cause a lifelong irreversible physical disability. Muscular spas-

ticity of such children causes an increase in an intra-abdominal pressure. Hiatal hernia is frequently complicated mainly due to high abdominal pressure and defective function of esophageal hiatus. Seizures, scoliosis, and respiratory distress can together promote the development of GER. The functional ability of the entire gastrointestinal tract gradually deteriorates with age, which also predisposes to GER development. Feeding problems and difficulty in swallowing are common.

In this study, patients were categorized into 3 groups. The first group consisted of otherwise normal infants who had symptoms suggesting the presence of GER or GERD. Patients in the second and the third groups were neurologically impaired except for one patient who had esophageal atresia and congenital esophageal stenosis repaired in early infancy. The patient was neurologically unimpaired, but had suffered from dysphagia and hematemesis for a long time due to reflux esophagitis. GER/GERD evaluation was performed in the second group because of the presence of

chronic symptoms suggesting GER or GERD, and it was performed as a preoperative examination of gastrostomy placement for nutritional support in the third group.

To detect GER and assess a possible relationship between GER and symptoms, a comprehensive investigation with several diagnostic studies is routinely performed. Barium contrast study of the upper gastrointestinal series is useful to detect anatomic abnormalities including hiatal hernia. However, it is not sensitive for the diagnosis of GER due to the short duration of the study. Esophageal pH monitoring is widely used and, so far, the most reliable method to sensitively detect pathologic acid reflux in the esophagus. It can measure the frequency and duration of acid reflux over 24-h period. The reflux index is defined as the percentage of time during which esophageal pH is less than 4.0. It reflects the cumulative exposure of gastric acid to the esophagus and is considered the most reliable marker for GER. Esophageal pH monitoring is also able to determine that symptoms are associated with acid reflux events when their timings are close or when the symptom index is high¹⁴⁾. However, since pH monitoring does not detect non-acid reflux, the reflux index may be within the normal limit regardless of the presence of reflux. Because of the usefulness and limitations of each diagnostic test, it was thought that a comprehensive work-up study is necessary to make diagnoses of GER and GERD, and that all the results of those studies should be taken into account when determining a patient's treatment.

Upper gastrointestinal endoscopy is recommended as the technique of choice in infants and children presenting with symptoms suggestive of reflux esophagitis^{10,11)}. While it is generally not indicated for uncomplicated GER, endoscopy is regarded as a useful tool to discover esophageal complications of GER such as reflux esophagitis, hemorrhage, stricture, Barrett's esophagus, and adenocarcinoma.

Reflux esophagitis is defined as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the gastroesophageal junction¹⁵⁾. A mucosal break is an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal looking mucosa, and the term was adopted since effective criteria for distinction between the endo-

scopic appearances of erosion and ulceration could not be defined¹⁶⁾. There is evidence that visible breaks in the mucosa are a reliable endoscopic finding of esophagitis¹⁵⁾. The modified LA classification is a grading system for the severity of esophagitis, and is useful for the evaluation of not only the severity of esophagitis but also the response to treatment^{12,17)}. Although this endoscopic classification is widely used, the system has not yet been validated in children. It seems that the classification is less pertinent in children since childhood reflux esophagitis is rarely as severe as in adults. The present study showed that the endoscopic grade of the modified LA classification was correlated with the results of 24-h pH monitoring. The reflux index, the number of long reflux episodes, and the duration of the longest reflux in patients with grade \geq B were significantly higher than those in patients with grade \leq M. In addition, postoperative esophageal endoscopy showed conspicuous improvements in mucosal lesions along with improvements in the reflux index after fundoplication. These results indicate that esophageal endoscopy and the modified LA grading system are useful in children as well, and therefore, it is appropriate to consider antireflux surgery based on the endoscopic findings with the results of other GER studies. It was also suggested that esophageal endoscopy was useful to monitor the effectiveness of treatment.

Regarding histology of mucosal specimens of the esophagus, there was no apparent correlation between the histology and clinical characteristics of the patients. Histologic criteria of reflux esophagitis, such as inflammatory cell infiltration and papillary elongation, could be evaluated in children, but the incidence of their appearance were not significantly different between the endoscopic grades. Although the incidences were low, it may be worthwhile to underscore that the sequelae of severe chronic GER, scar formation and Barrett mucosa, were observed only in patients with grade D esophagitis. Generally, the microscopic changes found with reflux esophagitis can be subdivided into epithelial alterations and inflammatory cell reactions¹⁰⁾. The presence of intraepithelial inflammatory cells, in particular eosinophils, is used for the diagnosis of esophagitis¹⁸⁾. Basal zone hyperplasia of the esophageal squamous epithelium exceeding 20% of the epithelial thickness and papillary elongation, that is, an increased

stromal papillary length extending into the upper-third of the epithelium, are widely accepted criteria for histologic diagnosis of reflux esophagitis^{10,19,20}. However, in children, there seems to be a poor correlation between endoscopic grades and histologic findings, and biopsies may not show histologic changes even in patients with severe erosive esophagitis or abnormal pH study, and vice versa^{21~23}. One of the explanations for this poor correlation is a patchy distribution of mucosal lesions²⁴. It is important to obtain appropriate tissue samples by visual inspection and multiple biopsies^{20,24}. Optimal orientation of biopsy specimens is necessary for precise histologic appraisal²⁵. It is known that histologic esophagitis cannot be identified in infants with GER who are younger than 4 months, and papillary elongation and intraepithelial eosinophils become more common with increasing age²². The results of the present study may suggest that the histologic criteria of reflux esophagitis in children should be re-evaluated. In the patients of this study, histology hardly contributed to our assessment of the severity of reflux esophagitis and indications for antireflux surgery. Mucosal biopsy, however, was not abandoned since it might be able to exclude esophagitis from other causes. A recent international consensus statement mentioned that microscopic changes present in GERD are not specific to reflux esophagitis and that the primary role for esophageal histology is to rule out other conditions in the differential diagnosis, including eosinophilic esophagitis, infectious esophagitis, Crohn's disease, and connective tissue diseases^{26,27}.

In conclusion, esophageal endoscopy is useful to examine the severity of reflux esophagitis and to monitor the effect of treatment in children with GER/GERD. The modified LA classification can be used for that purpose in children as well. Histologic evaluation of esophageal mucosa, although treatment is seldom influenced by the results, should be performed so that it may exclude other disorders in the differential diagnosis.

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