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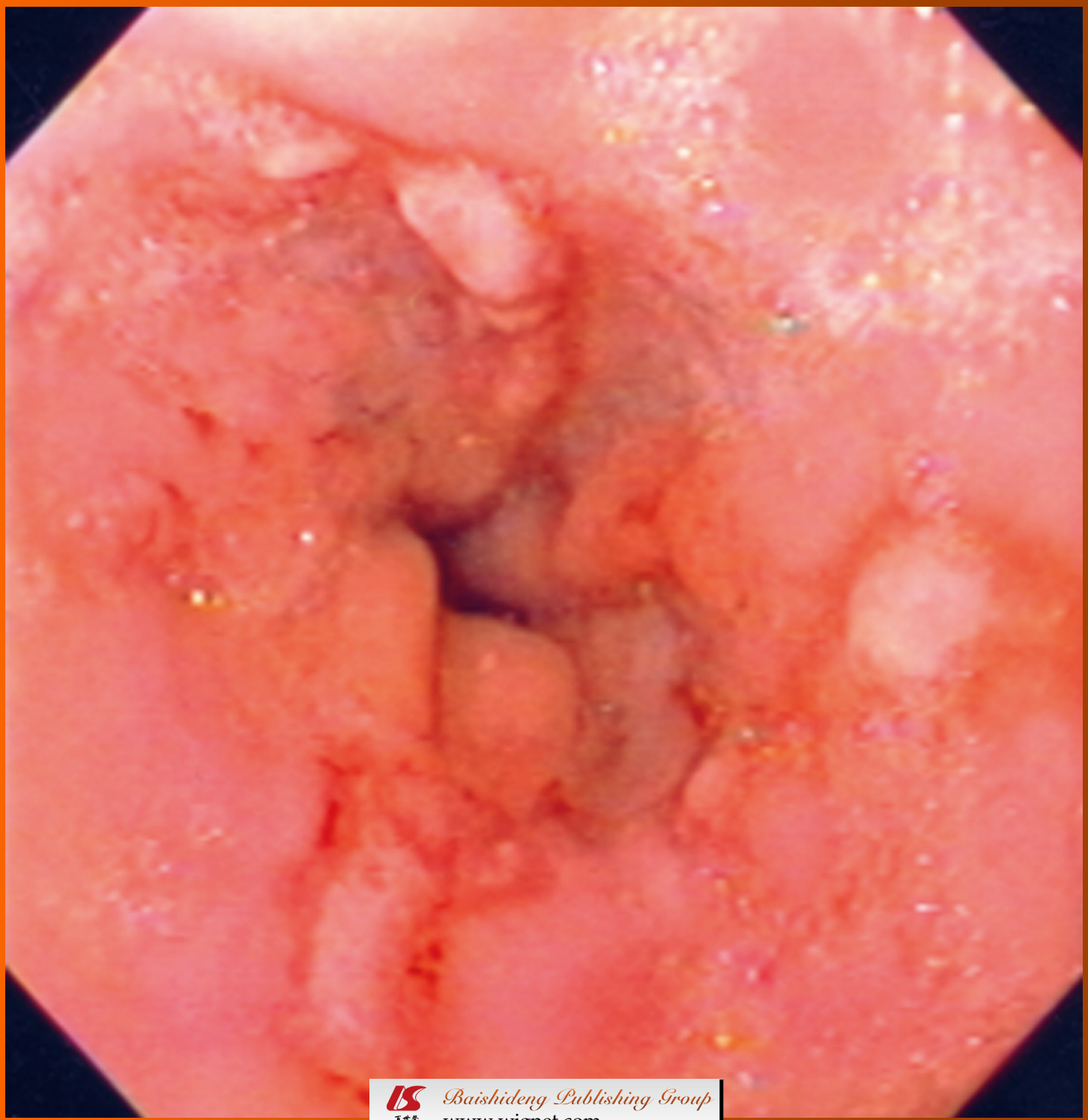

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TOPIC HIGHLIGHT

Fernando Fornari, Professor, *Series Editor*

Managing gastroesophageal reflux disease in children: The role of endoscopy

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Abstract

Gastroesophageal reflux disease (GERD) is a growing problem in the pediatric population and recent advances in diagnostics and therapeutics have improved their management, particularly the use of esophago-gastroduodenoscopy (EGD). Most of the current knowledge is derived from studies in adults; however there are distinct features between infant onset and adult onset GERD. Children are not just little adults and attention must be given to the stages of growth and development and how these stages impact the disease management. Although there is a lack of a gold standard test to diagnose GERD in children, EGD with biopsy is essential to assess the type and severity of tissue damage. To date, the role of endoscopy in adults and children has been to assess the extent of esophagitis and detect metaplastic changes complicating GERD; however the current knowledge points another role for the EGD with biopsy that is to rule out other potential causes of esophagitis in patients with GERD symptoms such as eosinophilic esophagitis. This review highlights special considerations about the role of EGD in the management of children with GERD.

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Key words: Endoscopy; Gastroesophageal reflux; Esophagitis; Infants; Children

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has a global impact on health and impairs the health related quality of life of a substantial proportion of the population worldwide. GERD is also prevalent in infants and adolescents suggesting that the disease process can begin early in life[1]. The disease phenotype in the pediatric population has changed over the last decades. For example, some complications such as esophageal strictures have decreased in prevalence and other complications such as extra-esophageal manifestations have been increasing. This might be in part explained by the great impact of new pharmacological therapies for GERD, but the most troubling complications of reflux disease in adults-esophageal adenocarcinoma-continues to increase at an alarming rate in some countries[2]. Therefore, the natural history of the disease needs more clarification.

GERD is a growing problem in pediatric population[1]. A database study involving children with GERD

in the United Kingdom between the years of 2000 and 2005 showed an incidence of GERD 0.84 per 1000 person-years[3]. The incidence decreased from 1-year age to 12-year age and further to that, it increased again reaching a maximum prevalence at age 16-17 (2.26 per 1000 person-years for girls and 1.75 per 1000 person-years for boys). Hiatus hernia, congenital esophageal abnormalities and neurologic impairment were risk factors. Although large prospective population-based studies are lacked, it has been suggested that many children who had GERD diagnosis continue to have symptoms in adolescence and as young adults[4].

The main difference between gastroesophageal reflux (GER) in the pediatric population and the adults is that spitting up, the most visible symptom of regurgitation in infants, occurs at least once per day in about 50% of the healthy 3- to 4-mo-old infants[5,6] and this leads up to 20% of caregivers in the United States seek medical help for this common behavior[5]. Regurgitation ameliorates spontaneously in most healthy infants by 12 mo to 18 mo of age[5-10]. When regurgitation occurs in an otherwise healthy infant with normal growth and development, this is the so called "physiologic GER" and lifestyle changes only are recommended to manage it[11] whereas GERD is defined when the reflux of gastric contents causes troublesome symptoms and/or complications[12].

Recently a consensus statement based on an extensive review of literature has been proposed by the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN) to provide pediatricians for the evaluation and management of patients with physiologic GER and GERD[11]. Therefore, the management of children with GERD is the focus of this review, particularly addressing the role of endoscopy.

DIAGNOSIS OF GERD

The diagnosis of GERD is often made clinically based on the symptoms or signs that may be associated with GER. In contrast with the adults, who can describe heartburn and/or regurgitation as typical GERD symptoms[13], subjective symptom description lacks reliability in infants and children younger than 8 to 12 years of age and consequently many of GERD symptoms in infants and children are nonspecific[11].

The main role of the medical history and physical examination in the evaluation of a child with GER is to rule out other worrisome disorders that present with vomiting (red flags-bilious vomiting, gastrointestinal bleeding, hematemesis, hematochezia, consistently forceful vomiting, onset of vomiting after 6 mo of life, failure to thrive, diarrhea, constipation, fever, lethargy, hepatosplenomegaly, bulging fontanelle, macro/microcephaly, seizures, abdominal distension) and to identify complications of GERD[11].

Although many tests have been used to diagnose GERD, the lack of a gold standard has hampered the assessment of the accuracy of various approaches to the diagnosis of GERD[14]. In addition, it is not known if a test can predict an individual patient's outcome. Nevertheless, tests are useful to detect pathologic reflux or its complications, to establish a causal relation between reflux and symptoms, to evaluate therapy, and to exclude other conditions. Because there is no test able to assess all those issues altogether, tests should be carefully selected according to the information sought, and the limitations of each test must be considered.

The tests more commonly available for the diagnosis of GERD in children are as follows[11]: (1) esophageal barium contrast radiography-not useful for the diagnosis of GERD but is useful to confirm or rule out anatomic abnormalities of the upper gastrointestinal tract, i.e., hiatal hernia; (2) esophageal pH monitoring-valid quantitative measure of esophageal acid exposure, useful to evaluate efficacy of anti- secretory therapy, but clinical utility of pH monitoring for diagnosis of extra-esophageal complications of GER are not well established; (3) esophageal combined multiple intraluminal impedance and pH monitoring-superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER, but clinical utility has yet to be determined; (4) esophageal manometry-may be useful to diagnose a motility disorder, i.e., achalasia or other esophageal motor abnormality that may mimic GERD; (5) esophago-gastroduodenoscopy (EGD) and biopsy-endoscopically visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux esophagitis; endoscopic biopsy is important to identify or rule out other causes of esophagitis, and to diagnose and monitor Barrett esophagus (BE); (6) esophago-gastric ultrasonography and nuclear scintigraphy-not recommended for the routine evaluation of GERD in children; and (7) empiric trial of acid suppression as a diagnostic test-a trial of pre-endoscopy proton pump inhibitors (PPIs) up to 4 wk may be helpful in an older child or adolescent with typical symptoms suggesting GERD. Specific multiple questionnaires have been developed in both adults and children to improve the accuracy of diagnosing GER[15,16]; however, many have limitations therefore they are not indicated for routine use[17,18].

EGD AND BIOPSY IN GERD

EGD allows direct visual examination of the esophageal mucosa and mucosal biopsies enable evaluation of the microscopic anatomy[19]. Endoscopic findings in patients with GERD include esophagitis, erosions, exudates, ulcers, strictures, hiatus hernia, and areas of possible esophageal metaplasia. A continuously patent gastro-esophageal junction (GEJ) seems to be helpful to predict esophagitis in biopsies[20].

Recent global consensus guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the GEJ[12,13,21]. The identification of esophagitis with

Table 1 Classification criteria and grading system of esophago-gastroduodenoscopy findings

Classification criteria	Grades	Findings
Hetzel-Dent[41]	0	Indicates no mucosal abnormalities
	1	Erythema, hyperemia, or mucosal friability without macroscopic erosions
	2	Superficial erosions involving less than 10% of the surface of the distal 5 cm of squamous epithelium
	3	Erosions or ulcerations involve 10%-50% of the mucosal surface of the distal 5 cm of squamous epithelium
	4	Deep ulceration anywhere in the esophagus or confluent erosion involving more than 50% of the mucosal surface of the distal 5 cm of squamous epithelium
Savary-Miller[42]	I	One or more supravestibular, nonconfluent reddish spots with or without exudates
	II	Erosive and exudative lesions in the distal esophagus that may be confluent, but not circumferential
	III	Circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudates
	IV	Presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia
Los Angeles[21]	A	One or more mucosal breaks, each ≤ 5 mm in length
	B	At least one mucosal break > 5 mm long, but not continuous between the tops of adjacent mucosal folds
	C	At least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential (< 75% of luminal circumference)
	D	Mucosal break that involves at least 75% of the luminal circumference

EGD has specificity 90%-95% for GERD[22], but has a poor sensitivity of around 50%[23]. About 50% of adult patients with GERD symptoms (i.e., heartburn and/or regurgitation) showed normal endoscopy in referral centers[24], but studies from community practice demonstrated that 53% to 70% of the patients had non erosive reflux disease (NERD)[25-29]. Erosive esophagitis (EE) does not seem to be as common as previously suggested in adults[30]. In regard of the pediatric population, a recent multicenter survey in 7188 children aged 0-17 years that underwent EGD showed 12.4% prevalence of EE[31] whereas a previous single center had showed 34.6% prevalence in 402 children[32]. The criticism for the studies in children is that patients who had EGD were not patients with GERD symptoms only, therefore the prevalence of EE in pediatric patients might be underestimated.

Acid suppression before EGD may significantly limit the sensitivity of endoscopy as a diagnostic tool. A recent study has shown that PPI use contributes significantly to the classification of GERD patients into the NERD-phenotype. NERD adults on PPI therapy demonstrate some features that are significantly different from PPI-naïve patients, but similar to EE patients. This observation supports the notion that some PPI-NERD patients are actually healed EE patients, and that an overlap does exist between the GERD phenotypes[33].

Evidence from adult studies indicates that visible breaks in the esophageal mucosa are the endoscopic signs of greatest interobserver reliability[34,35]. Operator experience is an important component of interobserver reliability[36,37]. Mucosal erythema or an irregular Z-line is not a reliable sign of reflux esophagitis[34,35]. Grading the severity of esophagitis, using a recognized endoscopic classification system, is useful for evaluation of the severity of esophagitis and response to treatment. Nevertheless, a recent study randomized patients with uncomplicated GERD to either empiric PPI therapy or endoscopy followed by treatment based on mucosal findings[38] and the result was that empiric therapy was more cost-effective. Although endoscopic determination of the grade of esophagitis can predict the expected healing response to antisecretory agents and the need for effective maintenance regimens[39], GERD treatment is typically guided by symptoms in adults, and thus determination of the grade of esophagitis for most clinical situations is not necessary[40].

The endoscopic classification criteria for GERD more frequently used in the pediatric setting are Hetzel-Dent[41] and Savary-Miller[42] classification (Table 1). Both have been used in several studies in children[43-49] whereas the Los Angeles classification[21] is generally used for adults, but it can be used also in children (Figure 1). Los Angeles and Hetzel-Dent scoring systems were reproducible in a study that evaluated intra- and inter-observer variability in the endoscopic scoring of esophagitis in adults[36]. However, a recent meta-analysis found significant difference in interpretation and comparison of healing rates for esophagitis among the three classification criteria (Hetzel-Dent, Savary-Miller, and Los Angeles)[50]. Therefore, in order to standardize the interpretation criteria, particularly focusing the healing criteria for a specific acid suppressant therapy, the Los Angeles criteria have been proposed as common criteria in adults and children[11,21].

The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of NERD or esophagitis of other etiologies[51-54]. Acid reflux episodes, volume, and acid clearance are important factors in the pathogenesis of reflux-induced lesions. Nonacid reflux is involved in the development of reflux symptoms in both NERD and EE patients[55]. The diagnostic yield of endoscopy is generally greater if multiple samples of good size and orientation are obtained from biopsy sites that are identified relative to major esophageal land marks[19,56,57].

There is insufficient evidence to support the use of histology to diagnose or exclude GERD[11]. Several variables have an impact on the validity of histology as a diagnostic tool for reflux esophagitis[54,58]. These include sampling error because of the patchy distribution of inflammatory changes and a lack in standardization of biopsy location, tissue processing, and interpretation of morphometric parameters. Histologic findings of elonga-

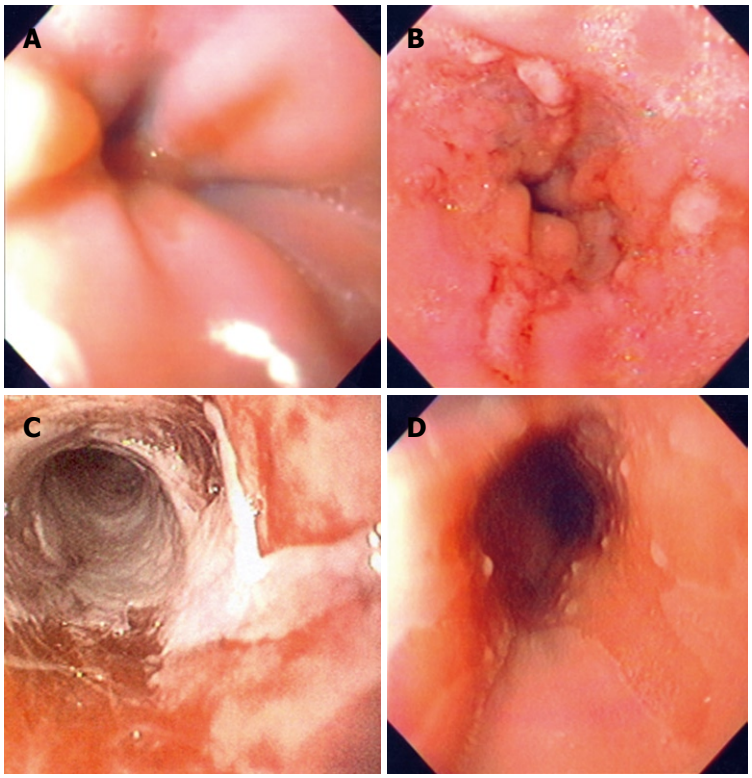

Figure 1 Endoscopy findings. A: Endoscopy of a child with esophagitis Los Angeles grade A showing one mucosal break < 5 mm in length; B: Another child with Los Angeles grade B showing 3 mucosal breaks > 5 mm long not continuous between the tops of adjacent mucosal folds; C: Endoscopy of a child with esophagitis Los Angeles grade D with mucosal break that involves at least 75% of the luminal circumference; D: Another 14-year-old patient with Barrett esophagus showing an area of endoscopically suspected esophageal metaplasia.

tion of papillae and basal hyperplasia are nonspecific reactive changes that may be found in esophagitis of other causes or in healthy volunteers[53,54,58-60].

The primary role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis (EoE), Crohn disease, BE, and infection[12,53]. EoE may have typical endoscopic features such as speckled exudates, trachealization of the esophagus, or linear furrowing; however in up to 30% of cases the esophageal mucosal appearance may be normal[51]. Two to 4 mucosal biopsy specimens of the proximal and distal esophagus should be obtained aiming diagnosis of EoE[52]. The number of eosinophils more than 15/phf is the major histological criterion of EoE[51,52]; however eosinophils have been found in a lower number in the esophageal mucosa of asymptomatic infants younger than 1 year of age[61], and in symptomatic infants with cow's milk-protein allergy[62].

Electron microscopy of esophageal biopsies suggested that dilated intercellular spaces might be an early marker of mucosal damage in GERD, which occurs in NERD patients irrespective of esophageal acid exposure[63,64]. These observations are important but remain research tools.

Finally, endoscopically visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux esophagitis. Mucosal erythema, pallor, and increased or decreased vascular pattern are highly subjective and nonspecific findings that are variations of normal. Histologic findings of eosinophilia, elongated papillae, basilar hyperplasia, and dilated intercellular spaces, alone or in combination, are insufficiently sensitive or specific to diagnose reflux esophagitis. Conversely, absence of these histologic changes does not rule out GERD. Endoscopic biopsy is important to identify or rule out other causes of esophagitis, and to diagnose and monitor BE and its complications.

EGD IN THE MANAGEMENT OF PEDIATRIC PATIENT WITH SUSPECTED GERD

Because the clinical presentation of GERD in infants is not restricted to typical symptoms (heartburn and/or regurgitation) as in older children, adolescents and adults, the several common signs or symptoms in whom an EGD is potentially helpful[11] are as follows.

Heartburn

A management approach to heartburn in older children and adolescents similar to that used in adults may be indicated[11,12]. If GERD is suspected as the most likely cause of symptoms, lifestyle changes, avoidance of precipitating factors, and a 2- to 4-wk trial of PPI are recommended[13]. If symptoms recur when therapy is discontinued,

EGD with biopsy may be helpful to diagnose esophagitis and rule out other causes, i.e., EoE that may present with heartburn[11].

Reflux esophagitis

Once reflux esophagitis is diagnosed, initial treatment for 2-3 mo with PPI is recommended. Patients who require higher PPI dose to control symptoms are those with conditions that predispose to severe-chronic GERD and those with higher grades of esophagitis or BE. In most cases, efficacy of therapy can be monitored by extent of symptom relief without routine endoscopic follow-up. Endoscopic monitoring of treatment efficacy may be useful in patients with atypical signs and symptoms, who have persistent symptoms despite adequate acid-suppressive therapy, or who had severe esophagitis at presentation[11].

BE

Esophageal metaplasia of the intestinal type occurs as a function of time and severity of reflux, which explains why it has not been described under 5 years of age and largely occurs over age 10 years[57]. Endoscopically suspected BE was rare (< 0.25%) in children and adolescents who underwent EGD[57], and older age and the presence of hypogonadotrophic hypogonadism (HH) were possible risk factors for BE[65]. BE occurs with greatest frequency in children with underlying conditions putting them at high risk for GERD. The groups of patients at high risk of chronic GERD are those with neurologic impairment, obesity, HH, esophageal atresia, and chronic respiratory disorders. In a group of selected children with severe-chronic GERD, columnar metaplasia was found in 5% and columnar metaplasia with goblet-cell metaplasia was present in another 5%[57]. The diagnosis of BE is both overlooked and overcalled in children[56,57] therefore it is important to accurately diagnose BE, especially in light of the proposed new criteria for the diagnosis of BE in children and adults[12,13]. This is of particular importance in children with severe esophagitis, in whom landmarks at endoscopy may be obscured by bleeding or exudate, or when landmarks are displaced by anatomic abnormalities or HH[19,56,57]. In these circumstances, a course of high-dose PPIs for at least 12 wk is advised to better visualize the landmarks in a following endoscopy[56]. When biopsies from ESEM show columnar epithelium, the term BE should be applied and the presence or absence of intestinal metaplasia specified[12,13,66].

EoE

EoE is a clinicopathological entity isolated to the esophagus characterized by a set of symptoms similar to GERD and eosinophilic infiltration of the esophageal epithelium. EoE represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Infants and toddlers often present with feeding difficulties, whereas school-aged children and are more likely to present with vomiting or pain, and adolescents with dysphagia. EoE in children is most often present in association with other manifestations of atopic diathesis (food allergy, asthma, eczema, chronic rhinitis, and environmental allergies). The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded. A subgroup of patients with EoE has been increasingly recognized as having PPI-responsive esophageal eosinophilia. These patients usually have typical EoE symptoms and GERD diagnostically excluded, but with clinicopathologic response to PPIs. It is important to establish the differential diagnosis among GERD, EoE and PPI-responsive esophageal eosinophilia as it implies distinct treatments. EGD with biopsy is currently the only reliable diagnostic test for EoE[52].

Dysphagia and food refusal

In the infant with feeding refusal, acid suppression without earlier diagnostic evaluation is not recommended. An upper gastrointestinal (GI) contrast study is useful but not required for the infant with feeding refusal or difficulty or the older child reporting dysphagia. Its major use is to identify a non-GERD disorder such as achalasia or foreign body or to identify esophageal narrowing from a stricture. In children and adolescents who report dysphagia or odynophagia EGD with biopsy is useful to distinguish among causes of esophagitis, *p.e.* EoE[11].

Child aged more than 18 mo with chronic regurgitation or vomiting

According to the natural history of GER, vomiting and regurgitation are less common in children older than 18 mo of age as these symptoms ameliorate after this age in the vast majority. Although these symptoms are not unique to GERD, evaluation to diagnose possible GERD and to rule out alternative diagnosis is recommended. Testing may include EGD, and/or esophageal pH/impedance monitoring, and/or barium upper GI series[11].

Infants with unexplained crying/distressed behavior

Few studies addressed the appropriate management of infants with irritability and reflux symptoms[67,68] and there is a lack of evidence to support an empiric trial of acid suppression therapy in infants with unexplained crying, irritability, or sleep disturbance. On the other hand, irritable infants may benefit from an empiric trial with hypoallergenic diet following diagnostic evaluations to rule out other conditions causing irritability[11,69,70]. However, if irritability persists with no explanation other than suspected GERD, additional investigations to assess the relationship between reflux episodes and symptoms or to diagnose reflux or other causes of esophagitis may be indicated. In such cases EGD, pH monitoring or impedance monitoring may be helpful[11].

EGD may be a useful tool to assess GER in children with other signs and symptoms suggestive of GERD such as apnea or apparent life threatening event; reac-

tive airways disease; recurrent pneumonia; upper airway symptoms; dental erosions; Sandifer syndrome. In all cases, a rational decision should be taken considering all the available tests other than endoscopy that could be helpful to the better management of a child with GERD.

NOVEL EGD TECHNOLOGIES

The role of newer endoscopic technologies-including narrow band imaging to enhance the contrast between esophageal and gastric mucosa, endoscopic functional luminal imaging probe to assess the esophagogastric junction compliance; videotelemetry capsule endoscopy, and ultra-thin unsedated transnasal endoscopy-for the diagnosis of GERD is controversial, primarily because of a lack of comparison with other validated tests[71,72]. No studies regarding these new techniques have been performed in children.

ENDOLUMINAL THERAPY OF GERD

Over the last decade, various endoluminal innovative techniques aiming to reduce reflux and GERD symptoms were enthusiastically developed. Endoluminal procedures have emerged as a new therapeutic option for GERD treatment: radiofrequency ablation to create submucosal thermal lesions in the smooth muscles of the lower esophageal sphincter (LES), injection of biopolymer substances into the muscular layer of the LES, and transmural plication and suturing devices to create pleats in the GEJ. The procedure devices were removed from the market by the manufacturers due to a variety of problems, including serious adverse events such as esophageal perforation and lack of efficacy[73-75]. Two techniques are currently being evaluated: radiofrequency (Stretta)[76] and full thickness plication or endoluminal fundoplication. Durability still needs to be determined for the sole technique that remains available (EsophyX)[77].

Regarding the pediatric population, few studies of endoluminal treatment for GERD have been performed in this group population. Endoluminal plication (EndoCinch) was performed in 17 patients aged 6-15 years. A sustained improvement in symptoms was seen at 3-year but not at 5-year follow up[78]. The endoluminal antireflux procedure (Stretta) was described in another series of patients aged 11-16 years[79], however long-term results are needed.

In conclusion, EGD has contributed greatly to the understanding and management of GERD and will continue to play an important role. New technology and better use of available resources such as more extensive and well informed use of histopathology is likely to yield better clinical results.

REFERENCES

1 **Vakil N**. Disease definition, clinical manifestations, epidemiology and natural history of GERD. *Best Pract Res Clin Gastroenterol* 2010; **24**: 759-764

2 **Ryan AM**, Duong M, Healy L, Ryan SA, Parekh N, Reynolds JV, Power DG. Obesity, metabolic syndrome and esophageal adenocarcinoma: epidemiology, etiology and new targets. *Cancer Epidemiol* 2011; **35**: 309-319

3 **Ruigómez A**, Wallander MA, Lundborg P, Johansson S, Rodriguez LA. Gastroesophageal reflux disease in children and adolescents in primary care. *Scand J Gastroenterol* 2010; **45**: 139-146

4 **El-Serag HB**, Gilger M, Carter J, Genta RM, Rabeneck L. Childhood GERD is a risk factor for GERD in adolescents and young adults. *Am J Gastroenterol* 2004; **99**: 806-812

5 **Nelson SP**, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997; **151**: 569-572

6 **Martin AJ**, Pratt N, Kennedy JD, Ryan P, Ruffin RE, Miles H, Marley J. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002; **109**: 1061-1067

7 **Hegar B**, Boediarso A, Firmansyah A, Vandenplas Y. Investigation of regurgitation and other symptoms of gastroesophageal reflux in Indonesian infants. *World J Gastroenterol* 2004; **10**: 1795-1797

8 **Miyazawa R**, Tomomasa T, Kaneko H, Tachibana A, Ogawa T, Morikawa A. Prevalence of gastro-esophageal reflux-related symptoms in Japanese infants. *Pediatr Int* 2002; **44**: 513-516

9 **Nelson SP**, Chen EH, Syniar GM, Christoffel KK. One-year follow-up of symptoms of gastroesophageal reflux during infancy. Pediatric Practice Research Group. *Pediatrics* 1998; **102**: E67

10 **Campanozzi A**, Boccia G, Pensabene L, Panetta F, Marseglia A, Strisciuglio P, Barbera C, Magazzù G, Pettoello-Mantovani M, Staiano A. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. *Pediatrics* 2009; **123**: 779-783

11 **Vandenplas Y**, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009; **49**: 498-547

12 **Sherman PM**, Hassall E, Fagundes-Neto U, Gold BD, Kato S, Koletzko S, Orenstein S, Rudolph C, Vakil N, Vandenplas Y. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol* 2009; **104**: 1278-1295; quiz 1296

13 **Vakil N**, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900-1920; quiz 1943

14 **Moayyedi P**, Talley NJ. Gastro-oesophageal reflux disease. *Lancet* 2006; **367**: 2086-2100

15 **Orenstein SR**, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire. *Clin Pediatr* (Phila) 1996; **35**: 607-614

16 **Kleinman L**, Rothman M, Strauss R, Orenstein SR, Nelson S, Vandenplas Y, Cucchiara S, Revicki DA. The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. *Clin Gastroenterol Hepatol* 2006; **4**: 588-596

17 **Lacy BE**, Weiser K, Chertoff J, Fass R, Pandolfino JE, Richter JE, Rothstein RI, Spangler C, Vaezi MF. The diagnosis of gastroesophageal reflux disease. *Am J Med* 2010; **123**: 583-592

18 **Dent J**, Vakil N, Jones R, Bytzer P, Schöning U, Halling K, Junghard O, Lind T. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. *Gut* 2010; **59**: 714-721

19 **Gillett P**, Hassall E. Pediatric gastrointestinal mucosal biopsy. Special considerations in children. *Gastrointest Endosc Clin N Am* 2000; **10**: 669-712, vi-vii
20 **Zion N**, Chemodanov E, Levine A, Sukhotnik I, Bejar J, Shaoul R. The yield of a continuously patent gastroesophageal junction during upper endoscopy as a predictor of esophagitis in children. *Dig Dis Sci* 2010; **55**: 3102-3107
21 **Lundell LR**, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172-180
22 **Richter JE**. Diagnostic tests for gastroesophageal reflux disease. *Am J Med Sci* 2003; **326**: 300-308
23 An evidence-based appraisal of reflux disease management--the Genval Workshop Report. *Gut* 1999; **44** Suppl 2: S1-16
24 **Ronkainen J**, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Graffner H, Vieth M, Stolte M, Engstrand L, Talley NJ, Agréus L. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005; **40**: 275-285
25 **Jones RH**, Hungin APS, Phillips J, Mills JG. Gastro-oesophageal reflux disease in primary care in Europe: Clinical presentation and endoscopic findings. *Eur J Gen Pract* 1995; **1**: 149-154
26 **Smout AJPM**. Endoscopy-negative acid reflux disease. *Aliment Pharmacol Ther* 1997; **11**: 81-85
27 **Lind T**, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, Stubberöd A. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997; **32**: 974-979
28 **Robinson M**, Earnest D, Rodriguez-Stanley S, Greenwood-Van Meerveld B, Jaffe P, Silver MT, Kleoudis CS, Wilson LE, Murdock RH. Heartburn requiring frequent antacid use may indicate significant illness. *Arch Intern Med* 1998; **158**: 2373-2376
29 **Fass R**, Fennerty MB, Vakil N. Nonerosive reflux disease--current concepts and dilemmas. *Am J Gastroenterol* 2001; **96**: 303-314
30 **Savarino E**, Zentilin P, Tutuian R, Pohl D, Casa DD, Frazzoni M, Cestari R, Savarino V. The role of nonacid reflux in NERD: lessons learned from impedance-pH monitoring in 150 patients off therapy. *Am J Gastroenterol* 2008; **103**: 2685-2693
31 **Gilger MA**, El-Serag HB, Gold BD, Dietrich CL, Tsou V, McDuffie A, Shub MD. Prevalence of endoscopic findings of erosive esophagitis in children: a population-based study. *J Pediatr Gastroenterol Nutr* 2008; **47**: 141-146
32 **El-Serag HB**, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. *Gastroenterology* 2001; **121**: 1294-1299
33 **Hershcovici T**, Fass R. Nonerosive Reflux Disease (NERD) - An Update. *J Neurogastroenterol Motil* 2010; **16**: 8-21
34 **Bytzer P**, Havelund T, Hansen JM. Interobserver variation in the endoscopic diagnosis of reflux esophagitis. *Scand J Gastroenterol* 1993; **28**: 119-125
35 **Vieth M**, Haringsma J, Delarive J, Wiesel PH, Tam W, Dent J, Tytgat GN, Stolte M, Lundell L. Red streaks in the oesophagus in patients with reflux disease: is there a histomorphological correlate? *Scand J Gastroenterol* 2001; **36**: 1123-1127
36 **Pandolfino JE**, Vakil NB, Kahrilas PJ. Comparison of inter- and intraobserver consistency for grading of esophagitis by expert and trainee endoscopists. *Gastrointest Endosc* 2002; **56**: 639-643
37 **Rath HC**, Timmer A, Kunkel C, Endlicher E, Grossmann J, Hellerbrand C, Herfarth HH, Lock G, Sahrbacher U, Schölmerich J, Kullmann F, Messmann H. Comparison of interobserver agreement for different scoring systems for reflux esophagitis: Impact of level of experience. *Gastrointest Endosc* 2004; **60**: 44-49
38 **Giannini EG**, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. *Am J Gastroenterol* 2008; **103**: 267-275
39 **Vigneri S**, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995; **333**: 1106-1110
40 **Kahrilas PJ**, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, Johnson SP, Allen J, Brill JV. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; **135**: 1383-1391, 1391.e1-1391.e5
41 **Hetzel DJ**, Dent J, Reed WD, Narielvala FM, Mackinnon M, McCarthy JH, Mitchell B, Beveridge BR, Laurence BH, Gibson GG. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988; **95**: 903-912
42 **Savary M**, Miller G. The esophagus. In: Savary M, Miller G, editors. Handbook and atlas of endoscopy. Solothurn: Verlag Gassman AG, 1978: 119-205
43 **Gunasekaran TS**, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 1993; **123**: 148-154
44 **Boccia G**, Manguso F, Miele E, Buonavolontà R, Staiano A. Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable? *Am J Gastroenterol* 2007; **102**: 1291-1297
45 **Hassall E**, Israel D, Shepherd R, Radke M, Dalväg A, Sköld B, Junghard O, Lundborg P. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. International Pediatric Omeprazole Study Group. *J Pediatr* 2000; **137**: 800-807
46 **Somani SK**, Ghoshal UC, Saraswat VA, Aggarwal R, Misra A, Krishnani N, Naik SR. Correlation of esophageal pH and motor abnormalities with endoscopic severity of reflux esophagitis. *Dis Esophagus* 2004; **17**: 58-62
47 **Madrazo-de la Garza A**, Dibildox M, Vargas A, Delgado J, Gonzalez J, Yañez P. Efficacy and safety of oral pantoprazole 20 mg given once daily for reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 2003; **36**: 261-265
48 **Van Biervliet S**, Van Winckel M, Robberecht E, Kerremans I. High-dose omeprazole in esophagitis with stenosis after surgical treatment of esophageal atresia. *J Pediatr Surg* 2001; **36**: 1416-1418
49 **Böhmer CJ**, Niezen-de Boer MC, Klinkenberg-Knol EC, Devillé WL, Nadorp JH, Meuwissen SG. The prevalence of gastroesophageal reflux disease in institutionalized intellectually disabled individuals. *Am J Gastroenterol* 1999; **94**: 804-810
50 **Yaghoobi M**, Padol S, Yuan Y, Hunt RH. Impact of oesophagitis classification in evaluating healing of erosive oesophagitis after therapy with proton pump inhibitors: a pooled analysis. *Eur J Gastroenterol Hepatol* 2010; **22**: 583-590
51 **Furuta GT**, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133**: 1342-1363
52 **Liacouras CA**, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic

esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011; **128**: 3-20.e6; quiz 21-22
53 **Dahms BB**. Reflux esophagitis: sequelae and differential diagnosis in infants and children including eosinophilic esophagitis. *Pediatr Dev Pathol* 2004; **7**: 5-16
54 **Dent J**. Microscopic esophageal mucosal injury in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2007; **5**: 4-16
55 **Savarino E**, Tutuian R, Zentilin P, Dulbecco P, Pohl D, Marabotto E, Parodi A, Sammito G, Gemignani L, Bodini G, Savarino V. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol* 2010; **105**: 1053-1061
56 **Hassall E**. Esophageal metaplasia: definition and prevalence in childhood. *Gastrointest Endosc* 2006; **64**: 676-677
57 **Hassall E**, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr* 2007; **150**: 262-267, 267.e1
58 **van Malenstein H**, Farré R, Sifrim D. Esophageal dilated intercellular spaces (DIS) and nonerosive reflux disease. *Am J Gastroenterol* 2008; **103**: 1021-1028
59 **Salvatore S**, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal reflux disease in infants: how much is predictable with questionnaires, pH-metry, endoscopy and histology? *J Pediatr Gastroenterol Nutr* 2005; **40**: 210-215
60 **Spechler SJ**, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 2007; **102**: 1301-1306
61 **Orenstein SR**, Shalaby TM, Kelsey SF, Frankel E. Natural history of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. *Am J Gastroenterol* 2006; **101**: 628-640
62 **Hill DJ**, Heine RG, Cameron DJ, Catto-Smith AG, Chow CW, Francis DE, Hosking CS. Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis. *J Pediatr* 2000; **136**: 641-647
63 **Caviglia R**, Ribolsi M, Maggiano N, Gabbrielli AM, Emerenziani S, Guarino MP, Carotti S, Habib FI, Rabitti C, Cicala M. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. *Am J Gastroenterol* 2005; **100**: 543-548
64 **Farré R**, Fornari F, Blondeau K, Vieth M, De Vos R, Bisschops R, Mertens V, Pauwels A, Tack J, Sifrim D. Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. *Gut* 2010; **59**: 164-169
65 **El-Serag HB**, Gilger MA, Shub MD, Richardson P, Bancroft J. The prevalence of suspected Barrett's esophagus in children and adolescents: a multicenter endoscopic study. *Gastrointest Endosc* 2006; **64**: 671-675
66 **Hassall E**. Cardia-type mucosa as an esophageal metaplastic condition in children: "Barrett esophagus, intestinal metaplasia-negative?". [corrected] *J Pediatr Gastroenterol Nutr* 2008; **47**: 102-106
67 **Jordan B**, Heine RG, Meehan M, Catto-Smith AG, Lubitz L. Effect of antireflux medication, placebo and infant mental health intervention on persistent crying: a randomized clinical trial. *J Paediatr Child Health* 2006; **42**: 49-58
68 **Moore DJ**, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *J Pediatr* 2003; **143**: 219-223
69 **Lucassen PL**, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: A double-blind, randomized, placebo-controlled trial. *Pediatrics* 2000; **106**: 1349-1354
70 **Hill DJ**, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol* 1995; **96**: 886-892
71 **Sharma P**, Wani S, Bansal A, Hall S, Puli S, Mathur S, Rastogi A. A feasibility trial of narrow band imaging endoscopy in patients with gastroesophageal reflux disease. *Gastroenterology* 2007; **133**: 454-464; quiz 674
72 **Amano Y**, Yamashita H, Koshino K, Ohshima T, Miwa H, Iwakiri R, Fujimoto K, Manabe N, Haruma K, Kinoshita Y. Does magnifying endoscopy improve the diagnosis of erosive esophagitis? *J Gastroenterol Hepatol* 2008; **23**: 1063-1068
73 **Hogan WJ**. Clinical trials evaluating endoscopic GERD treatments: is it time for a moratorium on the clinical use of these procedures? *Am J Gastroenterol* 2006; **101**: 437-439
74 **Louis H**, Devière J. Ensocopic-endoluminal therapies. A critical appraisal. *Best Pract Res Clin Gastroenterol* 2010; **24**: 969-979
75 **Vassiliou MC**, von Renteln D, Rothstein RI. Recent advances in endoscopic antireflux techniques. *Gastrointest Endosc Clin N Am* 2010; **20**: 89-101, vii
76 **Aziz AM**, El-Khayat HR, Sadek A, Mattar SG, McNulty G, Kongkam P, Guda MF, Lehman GA. A prospective randomized trial of sham, single-dose Stretta, and double-dose Stretta for the treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 818-825
77 **Velanovich V**. Endoscopic, endoluminal fundoplication for gastroesophageal reflux disease: initial experience and lessons learned. *Surgery* 2010; **148**: 646-651; discussion 651-653
78 **Thomson M**, Antao B, Hall S, Afzal N, Hurlstone P, Swain CP, Fritscher-Ravens A. Medium-term outcome of endoluminal gastroplication with the EndoCinch device in children. *J Pediatr Gastroenterol Nutr* 2008; **46**: 172-177
79 **Liu DC**, Somme S, Mavrelis PG, Hurwich D, Statter MB, Teitelbaum DH, Zimmermann BT, Jackson CC, Dye C. Stretta as the initial antireflux procedure in children. *J Pediatr Surg* 2005; **40**: 148-151; discussion 151-152

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TOPIC HIGHLIGHT

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Contribution of endoscopy in the management of eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a clinicopathological entity characterized by a set of symptoms similar to gastroesophageal reflux disease and eosinophilic infiltration of the esophageal epithelium. EoE is an emerging worldwide disease as documented in many countries. Recent reports indicate that EoE is increasingly diagnosed in both pediatric and adult patients although the epidemiology of this new disease entity remains unclear. It is unclear whether EoE is a new disease or a new classification of an old esophageal disorder. Esophagogastroduodenoscopy (EGD) and biopsies with histological examination of esophageal mucosa are required to establish the diagnosis of EoE, verify response to therapy, assess disease remission, document and dilate strictures and evaluate symptom recurrence of EoE. Repeated endoscopies with biopsies are necessary for monitoring of disease progression and treatment efficacy. EGD has a fundamental role in the diagnosis and management of EoE, forming an essential part of the investigation and follow-up of this condition. EoE is now considered a systemic disorder and not only a local condition with an important immunological background. One of the aims of research in EoE is to study non-invasive markers, such as immune indicators found in plasma, that correlate with local presence of EoE in esophageal tissues. Studies over the next few years will provide new information about diagnosis, pathogenesis, endoscopic/histologic criteria, non-invasive markers, novel and more efficacious treatments, as well as establishing natural history. Randomized clinical trials are urgently called for to inform non-invasive diagnostic tests, hallmarks of natural history and more efficacious treatment approaches for patients with EoE. The collaboration between pediatric and adult clinical and experimental studies will be paramount in the understanding and management of this disease.

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Key words: Eosinophilic; Esophagitis; Atopy; Endoscopy; Pediatrics

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INTRODUCTION

Eosinophilic gastrointestinal disorders are increasingly described diseases that are characterized by eosinophilic

infiltration and inflammation of the gastrointestinal tract in the absence of others identified causes of eosinophilia. These disorders include eosinophilic esophagitis (EoE), eosinophilicgastroenteritis, and eosinophilic colitis[1].

EoE is a clinical entity characterized by a set of symptoms similar to gastroesophageal reflux disease (GERD) with eosinophilic infiltration of the esophageal epithelium[2]. EoE is an emerging worldwide disease as documented in many countries[3-9]. During the last decade, pediatric and adult specialists including gastroenterologists, allergists and pathologists have published a multidisciplinary body of literature solidifying the position of EoE as a distinct clinicopathological entity[10].

With the accumulating data providing evidence that EoE appears to be an antigen-driven immunologic process with multiple pathogenic pathways, a new conceptual definition is proposed to highlight that EoE represents a chronic, immune/antigen-mediated disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-inflammation[11].

The primary symptoms of EoE are also observed in patients with chronic esophagitis. However, in contrast to GERD, EoE is typically associated with normal pH probe results, occurs more frequently in males (75% to 80%), and appears to have a common familial incidence and a high rate of association with atopic diseases[1-3].

EoE affects all age groups but it was first described in children because routine biopsies are common practice in pediatric gastroenterology[12,13]. Recent reports indicate that EoE is increasingly diagnosed in both pediatric and adult patients although the epidemiology of this new disease entity remains unclear[14].

Epidemiological data indicate that EoE is now the second leading cause of chronic esophagitis, after GERD, and is a frequent cause of dysphagia[15]. A potential genetic component is suggested not only by the male predominance, but also by the increased number of white people affected and the augmented incidence in familial cases[16]. Familial clusters of EoE have been described, although the exact susceptibility loci for familial and sporadic disease require further clarification[17].

The prevalence of EoE seems to be rising, although increased detection is likely to have contributed to a change in prevalence statistics. According to a recent review the number of new patients has increased on an annual basis[16]. The authors suggested that although the background to this rise of EoE remains unclear, it is probably similar to the increase seen in other atopic diseases such as asthma and atopic dermatitis[16,18].

A recent electronic survey demonstrated that EoE is diagnosed more often in northeastern American states and urban areas than in rural settings[19]. Another recent systematic review of published literature stated the prevalence of EoE in adult populations varies considerably. It is high in dysphagia patients, quite low in population-based studies and intermediate among unselected endoscopy patients[7].

DeBrosse *et al*[20] have recently demonstrated a dramatic increase of incidence of new cases of esophageal eosinophilia over a 17-year period in their institution, but when corrected for the large increase in the number of esophagogastroduodenoscopy (EGD) performed, there was a stable proportion of esophageal eosinophilia per EGD. They suggest that EoE is not a new disease but instead is a new classification of a persistent esophageal disorder[20].

According to guidelines, EoE can only be diagnosed by endoscopy and biopsy with the finding of 15 or more eosinophils per high-power field (hpf) of esophageal tissue after aggressive treatment for gastroesophageal reflux medications[1,2]. An updated consensus report noted important additions since the 2007-consensus including a new potential disease phenotype, proton pump inhibitor-responsive esophageal eosinophilia, and genetic modifications that included EoE susceptibility caused by polymorphisms in the thymic stromal lymphopoietin protein gene[11].

Endoscopic findings coupled to histology have been used to support a diagnosis of EoE, and to assess response to therapy. Some patients may need endoscopic dilations in the case of eosinophilic strictures.

The treatment of EoE in the majority of children relies on elemental diets or elimination of one or several food allergens. In older children and adults, treatment usually involves a topical corticosteroid or short courses of systemic steroids. Monitoring of treatment response requires repeated esophagogastroscopic examinations and esophageal biopsies[1,2,11].

There have been few randomized controlled trials investigating optimal EoE management, and currently there is a paucity of reliable prognostic data regarding the long-term outcome of untreated patients. Among the different therapeutic approaches suggested for EoE none has absolute advantages[18,19]. Options should therefore be chosen on a patient-by-patient basis given their characteristics, their sensitivity to various allergens and treatment responses. This multidisciplinary approach to EoE is fundamental because of the frequent association of EoE and atopical manifestations. Coordination of the work of gastroenterologists and allergologists is essential, and it is also very important to involve nutritional experts in cases of significant food restriction.

The dramatic increase in prevalence of EoE over the last decade provides clinicians with new explanations for previously unexplained food impaction, dysphagia, heartburn, chest pain, vomiting and abdominal pain in children and in adults. Clinicians are faced with complex issues regarding the diagnosis and optimal management of these often difficult-to-treat patients. This review highlights some important aspects of EoE and special considerations in the contribution of endoscopy in the management of the condition.

DIAGNOSIS OF EoE

According to the American Gastroenterological Association and the First International Gastrointestinal Eosino-

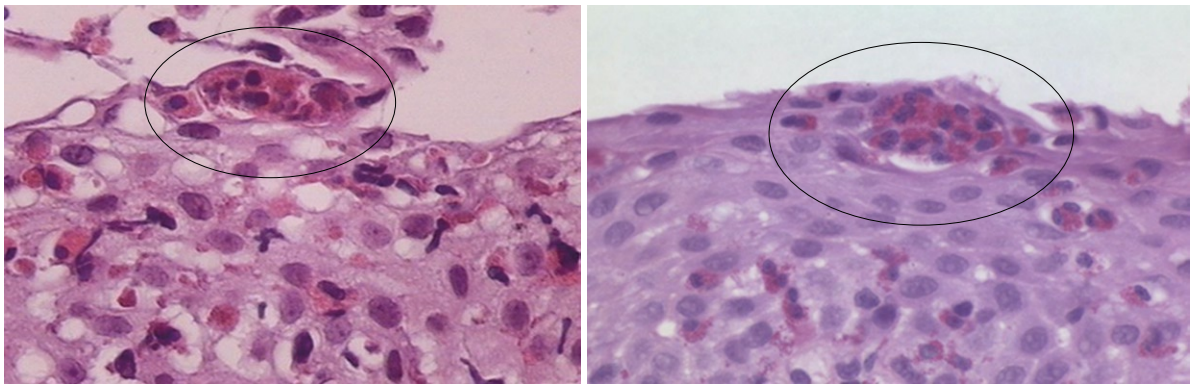

Figure 1 Eosinophilic microabscess in the esophageal superficial layer.

phil Research Symposium (FIGERS), as recommended by the consensus report, EoE is a clinicopathological entity and its diagnosis is dependent on the demonstration of high eosinophilic counts in esophageal biopsies from a patient with symptoms of esophageal dysfunction and the exclusion of GERD[1,2]. An increasing body of information describes a subset of patients whose symptoms and histological findings are responsive to proton pump-inhibitor (PPI) treatment and who might or might not have GERD[11]. The new guideline continues to define EoE as an isolated chronic disorder of the esophagus diagnosed by both clinical and pathological features but also describe a new disease phenotype, i.e., proton pump inhibitor-responsive esophageal eosinophilia[11].

The leading symptom of EoE in adolescents and adults is dysphagia for solids with the imminent risk of prolonged food impaction. Furthermore, patients frequently report retrosternal pain that is unrelated to swallowing activity. For this reason, esophageal biopsies should be taken to look for histological evidence of EoE in adult patients with unexplained dysphagia, even if results of endoscopy appear normal or identify other potential cause of dysphagia[11].

Clinical manifestations of EoE in infants and children are nonspecific and vary by age but are predominantly feeding difficulties[11]. The diagnostic guidelines regarding this disorder are evolving continuously as more is learned from ongoing research. However, diagnosis based on symptoms alone is not feasible. The clinical and histopathologic distinctions between EoE and GERD remain controversial and are based on limited data[20].

The number of eosinophils used to define EoE has varied widely in different publications and there are limited numbers of studies comparing patients with EoE and GERD[21]. Recent data report a substantial number of patients (30%) previously diagnosed with reflux esophagitis between 1982 and 1999 with histological evidence of EoE[20]. These patients were predominantly male and distinguished from patients with chronic esophagitis by a chief complaint of dysphagia[20]. Another important feature in the diagnosis is the absence of eosinophilia in others parts of gastrointestinal with mainly normal gastric and duodenal biopsies.

The diagnostic criteria have varied considerably not only in terms of eosinophil counts (5 to 30 eosinophils/hpf) but also in the definition of hpf, and the method of counting eosinophils[22].

Intraepithelial eosinophilia is considered the cardinal histopathological feature, although it is not limited to EoE, and may be seen in a variety of other conditions including GERD, drug-related esophagitis, infections, Crohn's disease, eosinophilic gastroenteritis[22]. Other characteristics including eosinophilic micro abscesses and involvement of the long esophageal segment, albeit in a patchy distribution, have been observed to be associated with EoE[22] (Figure 1). Reactive mucosal changes such as basal cell hyperplasia and papillary elongation are other important features that can also be associated with GERD but may be more pronounced in EoE[21,22]. Aceves *et al*[23] have found pan-esophageal eosinophilia associated with pan-esophageal basal zone hyperplasia. They showed in children that biopsy specimens with less than 5 eosinophils per hpf never demonstrated basal zone hyperplasia. Studies have documented submucosal fibrosis and subepithelial sclerosis as important features of EoE[22,24,25].

Recently Lee *et al*[22], comparing 23 cases of EoE compared to 20 cases of GERD in an adult cohort, found that EoE patients had significantly higher eosinophils counts in proximal (39.4 *vs* 0.6 eosinophils/hpf) and distal biopsies (35.6 eosinophils/hpf *vs* 1.9 eosinophils/hpf) with high eosinophils counts (> 15/hpf) in proximal biopsies being an exclusive feature of EoE (83% *vs* 0%).

It is recognized that EoE tends to involve the esophagus more proximally than GERD[22,26]. Another major EoE diagnostic finding in that study was subepithelial sclerosis[22]. While intense eosinophilic infiltration most probably represents EoE, the diagnostic dilemma lies in those patients with biopsies that show intermediate numbers of eosinophils (5-15/hpf). In these cases additional pathological diagnostic features are necessary[27].

The diagnosis of EoE remains the responsibility of the gastrointestinal endoscopist and the pathologist because confirmatory endoscopic biopsies from esophageal mucosa are still the only means of establishing the diagnosis and assessing the effectiveness of treat-

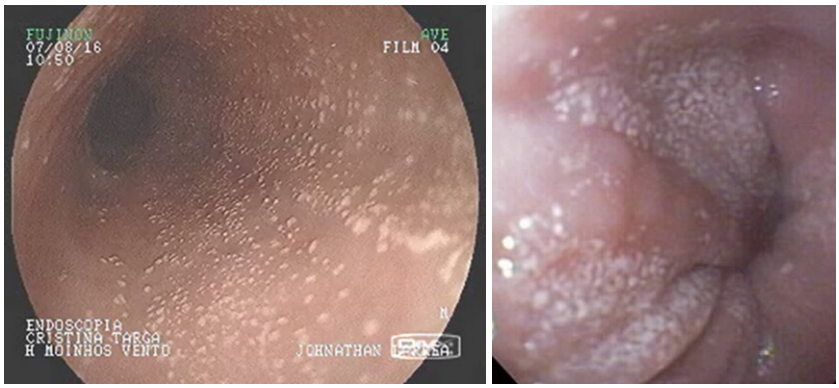

Figure 2 White specks in the mucosa of the esophagus.

ment. Because the range of eosinophil numbers in EoE and GERD varies considerably, the potential exists for esophagitis with more than 15 eosinophils/hpf in the esophageal mucosa to respond completely to antireflux therapy[11,22,27-29]. In that setting, the clinical diagnosis could therefore be "GERD with reflux esophagitis," despite the histological diagnosis of EoE, or according to the new guidelines it could be the phenotype "PPI-responsive esophageal eosinophilia". The number of eosinophils in reflux esophagitis is typically fewer than 7/hpf[27]. However, recent reports of children and adults who have large numbers of eosinophils consistent with EoE that responded to antireflux therapy lead us to be careful in assigning a clinical diagnosis[28,29]. This should be done only when additional information supports the diagnosis. Without clinical and pathologic follow-up EoE might well be overestimated[29]. Until more is known regarding this subgroup of patients, they should be given diagnoses of PPI-responsive esophageal eosinophilia[11]. Clinical judgment, as well as information derived from therapeutic response to PPI, impedance-pH monitoring, or both, should be taken into consideration to differentiate carefully between GERD-esophagitis and EoE[11].

PPI responsiveness or diagnostic testing (pH monitoring) might not adequately distinguish between GERD and EoE[11]. Future studies could help to determine whether PPIs may have a potential anti-inflammatory property or a barrier-healing role that helps to decrease an immune-antigen-driven response[11].

ENDOSCOPY FINDINGS IN EoE

EGD and biopsies with histological examination of esophageal mucosa are required to establish the diagnosis of EoE, verify response to therapy, assess disease remission, document and dilate strictures and evaluate symptom recurrence of EoE. EGD is an essential part of the investigation and follow-up of EoE[1].

In contrast to the variable history and characteristic histology, endoscopic abnormalities can be very suggestive of EoE, but can often be unremarkable or misleading[19,21]. EoE presents a variety of signs, evoking an endoscopic pattern that is neither disease specific nor consistent in a range of examinations[30]. In general, findings of endoscopic mucosal abnormalities are used to support or refute a diagnosis of EoE and they are very important in assessing the response to treatment[31].

Repeated EGDs are often required to assess the efficacy of any therapeutic intervention for EoE. In addition, endoscopy potentially allows dilatation of esophageal strictures.

Characteristic upper endoscopic features in EoE include mucosal friability, erythema and loss of vascularity, linear furrowing, white plaques or exudates, concentric rings (esophageal "trachealization"), delicate mucosa (crepe-paper mucosa) prone to tearing and diffuse luminal narrowing or strictures. Another important finding of EoE is eosinophilic infiltrates in endoscopically normal esophagus. Significant intraepithelial eosinophilia can be found in about one third of patients with grossly unremarkable mucosa[3,32].

White mucosal plaques are a common feature, reflecting fibrinous exudates due to epithelial eosinophilic inflammation (Figure 2). Although the exact etiology is not known, the plaques are thought to represent eosinophilic abscesses on the surface of the esophageal mucosa. They may be mistaken for esophageal candidiasis and esophageal biopsies (culture) are, therefore, necessary to differentiate these disorders. While not pathognomonic, rings, linear furrows, or white plaques on endoscopy are very suggestive of EoE (Figure 3). The presence or absence of these endoscopic findings is used by most gastroenterologists, in making a diagnosis of EoE, to guide biopsy decisions, and to assess a patient's response to therapy. It is still unclear whether endoscopists can reliably and accurately identify these findings. While the exact cause of the furrowing and ring-like formation is unknown, they are thought to represent tissue edema, inflammation and possible fibrosis. Chronic inflammation is of concern as it may cause progressive scarring, strictures, and potentially result in permanent narrowing of the esophagus[29,32]. Liacouras *et al*[3] reported retrospectively on a total of 381 pediatric patients (66% male, age 9.1 ± 3.1 years) who were diagnosed with EoE; 312 presented with symptoms of gastroesophageal reflux and 69 with dysphagia. Endoscopically, 68% of patients had a

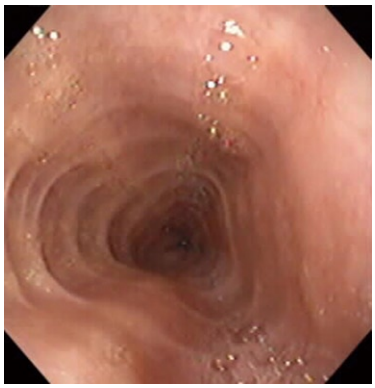

Figure 3 Rings in esophageal mucosa in eosinophilic esophagitis.

visually abnormal esophagus: 41% had vertical lines, 12% had concentric rings, and 15% had white specks. Among those patients, 32% had a normal-appearing esophagus despite severe histological esophageal eosinophilia. The average numbers of esophageal eosinophils (per 400 × hpf) proximally and distally were 23.3 ± 10.5 and 38.7 ± 13.3, respectively[3].

In a retrospective study of 29 patients from southern Brazil with a median age of 7 years (76% male) we have found 24% with a normal-appearing esophagus, 48% with vertical furrowing, 41% with white mucosal plaques, and only 7% with concentric rings[6]. Several patients presented more than one feature as white specks and linear furrowing (Figures 4 and 5).

The FIGERS consensus guideline recommend taking several biopsies from different levels along the length of the esophagus, regardless of its macroscopic appearance[1]. Lower esophageal eosinophilia is common in GERD, and further counting of eosinophils in the proximalmucosa is needed to differentiate between GERD and EoE.

The patchy eosinophilic infiltration in proximal and distal esophageal mucosa is very important in the differential diagnosis with GERD. Therefore biopsies should be taken from several esophageal levels. Biopsies from stomach and duodenum should also be obtained to allow differentiation between EoE and a more widespread eosinophilic gastroenteritis[1,2]. It is noteworthy that a normal esophageal appearance does not rule out EoE[1-3].

A remaining unresolved question is which endoscopic signs reflect acute inflammation, and are therefore potentially reversible, and which signs persist despite successful treatment of the inflammation and are thus a possible manifestation of esophageal remodeling[15]. EoE may also be ascertained incidentally in patients undergoing endoscopy for other reasons.

One recent study was conducted to assess inter- and intraobserver reliability of endoscopic findings with white-light endoscopy and further adding narrow band imaging (NBI)[21]. Gastroenterologists identified rings and furrows with fair to good reliability, but did not reliably identify plaques or normal images. Intraobserver agreement varied and NBI did not improve endoscopic recognition. The conclusion was that endoscopic findings might not be reliable for supporting a diagnosis of EoE or for making treatment decisions[21]. Another report assessing the value of confocal laser endomicroscopy with video for the *in vivo* diagnosis of EoE has indicated the potential of this technique for the diagnosis of this new entity[33].

In terms of histology, the counting of eosinophils can be problematic because they often lie just under the luminal surface of the esophagus in EoE, and their number may be underestimated from a poorly oriented section in which the immediate subluminal area is outside the sample. The eosinophilia in EoE can be remarkably patchy, particularly during treatment. It is not unusual to have an abnormal biopsy specimen taken millimeters from another specimen that is completely normal.

Studies in adults with EoE have established that six biopsies taken from the esophagus are enough for diagnosis. Fewer biopsies can miss the diagnosis because of sampling errors[25,34]. By using 15 eosinophils/hpf as a threshold for diagnosis, one study identified that the sensitivity of a single biopsy was 73% and increased to 84%, 97% and 100% when taking 2, 3 and 6 biopsies, respectively[35]. According to the latest guidelines, 2 to 4 mucosal biopsies specimens of the proximal and distal esophageal mucosa should be obtained[11]. Long-standing disease tends to create a ringed appearance, more common in the adult population with EoE. In addition, strictures, diffuse narrowing (so-called "small-caliber esophagus"), and friability of the epithelium, such that it longitudinally tears with passage of the scope (tissue paper mucosa), can be features of more long duration EoE.

Repeat endoscopy at appropriate intervals is needed to determine whether the inflammation has completely abated, irrespective of the therapy initiated. Symptoms can resolve in 2 to 4 wk, regardless of the type of treatment, but this is an unreliable measure of inflammation because the absence of symptoms does not assure the absence of inflammation. Histological response to topical steroids is generally complete in 4 to 12 wk. Histological response to dietary antigen elimination can be seen in 4 to 8 wk but is remarkably variable, having taken more than 4 mo in some individuals[27].

Evidence-based guidelines on the frequency of follow-up endoscopy have not been published, and frequency varies in clinical practice. In some practices the endoscopy is repeated 12 wk after diet or medication change, allowing sufficient time for a response to develop[27]. Incomplete responses are difficult to interpret and often require extension of the trial and repeated endoscopy to access the impact of therapy before changing the protocol[27]. Successful therapy results in complete resolution of the inflammation. When partial responses occur they must be evaluated for the necessity of more aggressive or alternative therapy, depending on the degree of remaining inflammation.

Chronic and active EoE is associated with tissue remodeling, manifest as deposition of dense collagen in the lamina propria. There is risk for the development of

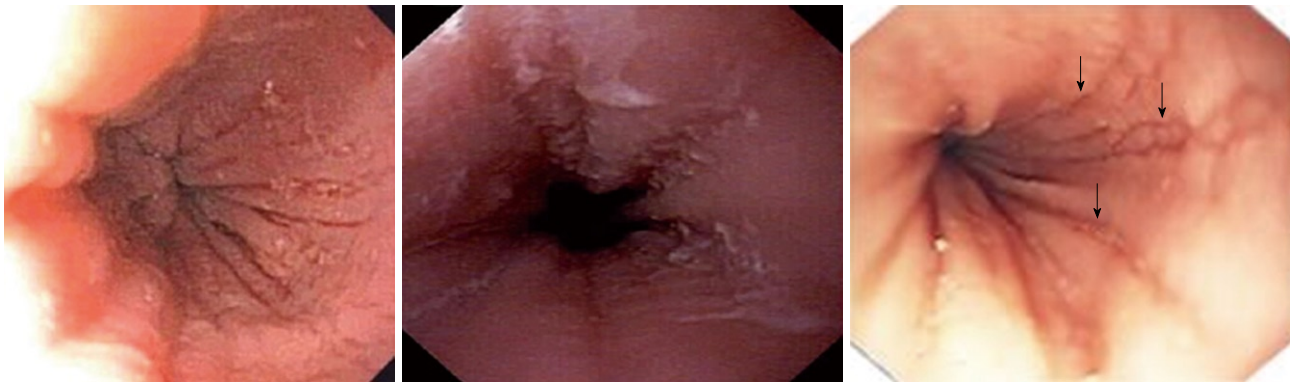

Figure 4 Linear furrowing in the esophageal mucosa.

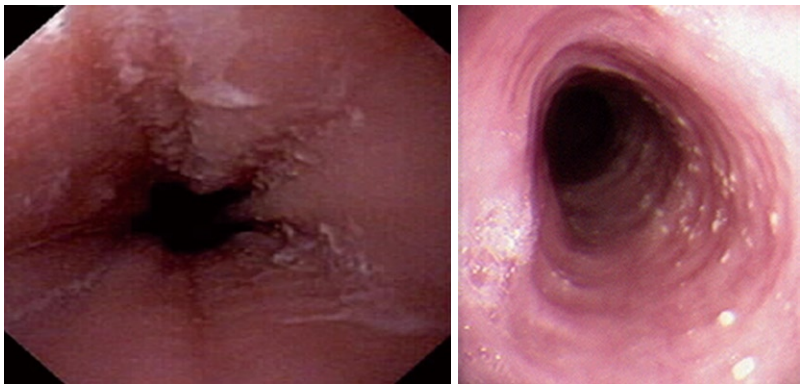

Figure 5 White specks and linear furrowing in the esophageal mucosa.

small-caliber esophagus and strictures, both of which have been observed as consequences of EoE in children and adults[30]. Assuring that esophageal histology has returned to normal seems to be an essential part of the management of each patient, to prevent further injury to the esophagus. Endoscopic re-evaluation after diet or medication changes determines whether a specific therapy has achieved a complete histological response and forms the basis for future management, with the goal of maintaining clinical and histological remission to avoid long-term complications such as esophageal stricture formation[27].

Some subjects with more severe disease present with severe structuring, furrowing, and ortrachealization, or food impaction which may need mechanical dilation of the esophagus. Endoscopic dilation should only be considered in cases with persistent symptoms and reduction in the caliber of the esophagus that have failed to respond to medical therapies. After instrumentation, tearing of the esophagus may occur in patients with moderate to severe inflammation. The mucosa may be extremely friable and may tear simply with the introduction of an endoscope during a routine diagnostic study because of the underlying edema and fibrosis. More significant tears have been reported in patients with small caliber esophagus or in patients undergoing esophageal dilatation.

EoE has been associated with an increased risk of esophageal mucosal tears induced by vomiting to dislodge impacted food. However, Boerhaave's syndrome or transmural perforation of the organ resulting from vomiting induced to dislodge impacted food has rarely been reported[36]. This rare complication of EoE has been documented in 13 reports, predominantly affecting young men in whom EoE had not been previously diagnosed, despite the majority having esophageal symptoms and a history of atopy[36]. There are only two published cases of esophageal perforation in children, and these were managed conservatively. Esophageal perforation caused by vomiting is a potentially severe complication of EoE that is being increasingly described in literature. Therefore, patients with non-traumatic Boerhaave's syndrome should be assessed for EoE, especially if they are young men who have a prior history of dysphagia and allergic manifestations[36].

The long-term consequences of esophageal eosinophilic infiltration, fibrous remodeling or possible modification using different therapies are controversial. For these reasons, it is difficult to recommend common guidelines for all patients although EoE should be considered a chronic disease with intermittent symptoms, persistent histological inflammation which affects patients quality-of-life[30]. Current guidelines suggest repeated biopsies for monitoring of disease progress and treatment efficacy. Since repeated endoscopy with biopsy entails risks to patients and costs to the medical system, the current aim is to study immune markers in plasma that correlate with a local presence in esophageal tissues in EoE subjects.

CLINICAL AND PATHOLOGICAL FEATURES DISTINGUISHING EOE FROM GERD

Because EoE and GERD cannot be differentiated on the basis of eosinophil counts alone, it can be a challenge to distinguish these disorders[21]. GERD and EoE need to be distinguished as they do not respond, in most of patients, to the same treatment[34]. Patients with EoE present with symptoms similar to those of GERD along with dense esophageal eosinophilia (with normal gastric and duodenal biopsies)[1,2]. Acid-induced esophagitis as a manifestation of GERD is the most frequent confounding diagnosis because reflux esophagitis may coexist with clinical EoE or mimic it histologically on hematoxylin- and eosin-stained sections. Few mast cells are present in reflux esophagitis, which may help in discriminating it from EoE at presentation provided special stains are applied to identify them, as they are not distinguishable on hematoxylin- and eosin-stained sections[37,38]. Some studies have identified increased numbers of mast cells in EoE patients in comparison to patients with GERD[39]. In the same way, EoE shows degranulating and active eosinophils in esophageal epithelium and molecular studies show specific up-regulated genes. Microarray analysis reveals signature panels which are distinct between patients with GERD and EoE[37,38].

Given to the coexistence of GERD in many cases of EoE and the effect shown by acid secretion inhibitors in controlling symptoms, in cases of suspected EoE, it is appropriate to carry out a therapeutic test using high dose PPIs over a period of 8 wk before repeating the endoscopy and taking further biopsies. This measure could correctly characterize those patients in whom EoE and GERD coexist and, in addition, would be better than monitoring the esophageal pH for ruling out GERD as the cause of eosinophilia[34,40]. It is only be possible to propose specific treatment for EoE when the persistence of the eosinophilic inflammatory infiltrate and the symptoms deriving from it continue in spite of previous acid blockade[41].

In the latest guidelines the inclusion of the new phenotype "PPI-responsive esophageal eosinophilia" challenges these concepts because therapeutic and basic studies as well as clinical experience have identified a potential anti-inflammatory or barrier-healing role for proton pump inhibition in patients with esophageal eosinophilia[11]. Potential explanations include healing of a disrupted epithelial barrier to prevent further immune activation, decreased eosinophil longevity, inherent anti-inflammatory proprieties of PPIs, or unreliable diagnostic testing[11]. According to current guidelines, responsiveness to PPI therapy rules out EoE. However, this statement is being questioned, since recent reports have indicated *in vitro* anti-inflammatory effects of PPIs, independent of acid suppression[29]. Cortes *et al*[42] demonstrated that omeprazole improved murine asthma by down-regulating interleukin (IL)-4, IL-13 and signal transducer and activator of transcription factor 6. Zhang *et al*[43] have demonstrated that PPIs suppress IL-13-induced eotaxin-3 expression by the acid-independent mechanism.

Currently, neither histopathology nor distribution of inflammatory changes in esophageal biopsies predicts response to PPI treatment[11]. Eosinophilic microabscesses and superficial layering of eosinophils are more typical of findings associated with EoE than GERD[11].

Features of GERD can coexist with EoE. Because of this, separating the 2 disorders into distinct diseases may be very difficult. Several theories regarding this interaction have been proposed: GERD causes esophageal injury with subsequent development of esophageal eosinophilic infiltration; GERD and EoE coexist but are unrelated; because of esophageal inflammation, EoE causes or contributes to the development of secondary GERD (poor motility); GERD causes mucosal disruption contributing to the development of EoE[44].

The high frequency of GERD described in adult populations with EoE suggests that there may be more than a chance association between the two conditions[44]. A trial of PPIs, even when diagnosis of EoE is clear-cut, is recommended[44]. However, on some occasions PPI responsiveness as well as diagnostic testing might not be helpful in distinguish between GERD and EoE[11].

Dellon *et al*[45] performed the largest retrospective clinical, endoscopic, and histological case-control study on data collected from 2000 to 2007 to differentiate between GERD and EoE. Data from 151 patients with EoE and 226 with GERD were analyzed. Features that independently predicted EoE included younger age, symptoms of dysphagia, documented food allergies, observations of esophageal rings, linear furrows, white plaques, or exudates and an absence of a hiatal hernia by upper endoscopy. In biopsy specimens, a higher maximum eosinophil count and the presence of eosinophil degranulation were observed[45].

The identification of histological features of EoE in nearly 30% of patients previously given diagnoses of reflux esophagitis suggests that EoE might have been under-diagnosed in the 1980s and 1990s[20]. On the other hand, Molina-Infante *et al*[29] demonstrated 75% of unselected patients and 50% with an EoE phenotype responding to PPI therapy. They stated that patients with PPI-responsive eosinophilic infiltration are phenotypically indistinguishable from EoE patients, thereby overestimating EoE[29]. Dohil *et al*[46] have recently suggested that patients with PPI-responsive esophageal eosinophilia should have ongoing monitoring for EoE during PPI monotherapy because this is a transient phenomenon. A database search revealed children who had an initial histological response to PPI monotherapy but had recurrence of esophageal eosinophilia and symptoms despite continued PPI therapy.

Additional follow-up studies are needed to better delineate EoE and GERD. In the pediatric EoE population is important to define disease behavior and to assess whether pediatric and adult EoE represent a continuum.

CONCLUSION AND FUTURE RECOMMENDATIONS

The endoscopic data concerning EoE represent a distinctive pattern of nonerosive inflammatory disease that can involve superficial or deep esophageal layers and present with a variety of clinical symptoms. Early recognition of these findings and their variability may lead to improved care of patients who have EoE. Upper endoscopy with biopsies is essential for the diagnosis, and for assessing the follow up of these patients. It is therefore crucial for the endoscopist to become familiar with the clinical and endoscopic EoE findings to ensure correct diagnosis and treatment.

Emerging data has increased our knowledge of EoE but important questions remain unanswered. Over the last decade pediatric and adult clinicians have published a multidisciplinary body of information confirming EoE as a distinct clinicopathological entity. Significant diagnostic, therapeutic and prognostic uncertainties are still associated with EoE, because it is a relatively recently discovered medical condition[11].

Basic science has in recent years unraveled some of the underlying pathological mechanisms of EoE, which lead to eosinophil recruitment, infiltration and activation as well as lesions in the esophagus. However, it is not yet clear which patient characteristics are associated with an increased risk of stricturing disease and whether lower degrees of symptoms or eosinophilic infiltration deserve treatment at all. Controversy remains as to whether histology and endoscopic findings should aim for complete mucosal remission, eosinophilic clearance or merely for symptomatic control, There are many remaining issues which cannot be resolved based on current published knowledge. These include the definition of EoE phenotypes allowing clear differentiation between EoE and GERD.

Subjects with EoE have different immune indicator profiles in blood plasma, peripheral blood mononuclear cells, and local esophageal tissue from subjects with GERD, ulcerative colitis, Crohn's disease, and healthy controls. This suggests that EoE is not only a local condition but also a systemic disorder that may be detected through analysis of plasma samples[47]. These indicators could serve in the near future as surrogate non-invasive markers that could be a useful substitute for endoscopy and biopsies[47]. Some authors, for example, have recently demonstrated that fibroblast growth factors may play an important role in the pathophysiology of EoE and may be part of a set of immune indicators that could, without biopsy, differentiate EoE subjects from subjects with other clinically similar symptoms such as GERD[47].

Future studies will provide new information about diagnosis, pathogenesis, endoscopic /histological criteria, non-invasive markers and novel and more efficacious treatments, as well as establishing natural history. Randomized clinical trials are urgently needed to inform non-invasive diagnostic tests, hallmarks of natural history and more efficacious treatment approaches for patients with EoE[12]. The collaboration between pediatric and adult clinical and experimental studies will be paramount in the understanding and management of this disease.

REFERENCES

1 **Liacouras CA**, Bonis P, Putnam PE, Straumann A, Ruchelli E, Gupta SK, Lee JJ, Hogan SP, Wershil BK, Rothenberg ME, Ackerman SJ, Gomes I, Murch S, Mishra A, Furuta GT. Summary of the First International Gastrointestinal Eosinophil Research Symposium. *J Pediatr Gastroenterol Nutr* 2007; **45**: 370-391

2 **Furuta GT**, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133**: 1342-1363

3 **Liacouras CA**, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005; **3**: 1198-1206

4 **Cherian S**, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006; **91**: 1000-1004

5 **Spergel JM**, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, Liacouras CA. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009; **48**: 30-36

6 **Ferreira CT**, Vieira MC, Vieira SM, Silva GS, Yamamoto DR, Silveira TR. [Eosinophilic esophagitis in 29 pediatric patients]. *Arq Gastroenterol* 2008; **45**: 141-146

7 **Sealock RJ**, Rendon G, El-Serag HB. Systematic review: the epidemiology of eosinophilic oesophagitis in adults. *Aliment Pharmacol Ther* 2010; **32**: 712-719

8 **Prasad GA**, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, Locke GR, Talley NJ. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009; **7**: 1055-1061

9 **Straumann A**, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; **115**: 418-419

10 **Lee JJ**, Furuta GT. Upper gastrointestinal tract eosinophilic disorders: pathobiology and management. *Curr Gastroenterol Rep* 2006; **8**: 439-442

11 **Liacouras CA**, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011; **128**: 3-20.e6; quiz 21-22

12 **Allen KJ**, Heine RG. Eosinophilic esophagitis: trials and tribulations. *J Clin Gastroenterol* 2011; **45**: 574-582

13 **Fox VL**, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. *Gastrointest Endosc* 2002; **56**: 260-270

14 **Enns R**, Kazemi P, Chung W, Lee M. Eosinophilic esophagitis: clinical features, endoscopic findings and response to treatment. *Can J Gastroenterol* 2010; **24**: 547-551

15 **Straumann A**, Conus S, Degen L, Felder S, Kummer M, Engel H, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010; **139**: 1526-137, 1537.e1

16 **Franciosi JP**, Tam V, Liacouras CA, Spergel JM. A case-

control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2009; **7**: 415-419
17 **Collins MH**, Blanchard C, Abonia JP, Kirby C, Akers R, Wang N, Putnam PE, Jameson SC, Assa'ad AH, Konikoff MR, Stringer KF, Rothenberg ME. Clinical, pathologic, and molecular characterization of familial eosinophilic esophagitis compared with sporadic cases. *Clin Gastroenterol Hepatol* 2008; **6**: 621-629
18 **Cianferoni A**, Spergel JM. Food allergy: review, classification and diagnosis. *Allergol Int* 2009; **58**: 457-466
19 **Spergel JM**, Book WM, Mays E, Song L, Shah SS, Talley NJ, Bonis PA. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. *J Pediatr Gastroenterol Nutr* 2011; **52**: 300-306
20 **DeBrosse CW**, Collins MH, Buckmeier Butz BK, Allen CL, King EC, Assa'ad AH, Abonia JP, Putnam PE, Rothenberg ME, Franciosi JP. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982-1999. *J Allergy Clin Immunol* 2010; **126**: 112-119
21 **Dellon ES**, Aderoju A, Woosley JT, Sandler RS, Shaheen NJ. Variability in diagnostic criteria for eosinophilic esophagitis: a systematic review. *Am J Gastroenterol* 2007; **102**: 2300-2313
22 **Lee S**, de Boer WB, Naran A, Leslie C, Raftopoulous S, Ee H, Kumarasinghe MP. More than just counting eosinophils: proximal oesophageal involvement and subepithelial sclerosis are major diagnostic criteria for eosinophilic oesophagitis. *J Clin Pathol* 2010; **63**: 644-647
23 **Aceves SS**, Newbury RO, Dohil R, Schwimmer J, Bastian JF. Distinguishing eosinophilic esophagitis in pediatric patients: clinical, endoscopic, and histologic features of an emerging disorder. *J Clin Gastroenterol* 2007; **41**: 252-256
24 **Parfitt JR**, Gregor JC, Suskin NG, Jawa HA, Driman DK. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. *Mod Pathol* 2006; **19**: 90-96
25 **Chehade M**, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007; **45**: 319-328
26 **Gonsalves N**, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006; **64**: 313-319
27 **Putnam PE**. Evaluation of the child who has eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2009; **29**: 1-10, vii
28 **Ngo P**, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus--peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006; **101**: 1666-1670
29 **Molina-Infante J**, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, Dueñas C, Fernandez-Gonzalez N, Quintana EM, Gonzalez-Nuñez MA. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011; **9**: 110-117
30 **Straumann A**. The natural history and complications of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008; **18**: 99-118; ix
31 **Peery AF**, Cao H, Dominik R, Shaheen NJ, Dellon ES. Variable reliability of endoscopic findings with white-light and narrow-band imaging for patients with suspected eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011; **9**: 475-480
32 **Chang F**, Anderson S. Clinical and pathological features of eosinophilic oesophagitis: a review. *Pathology* 2008; **40**: 3-8
33 **Neumann H**, Vieth M, Atreya R, Mudter J, Neurath MF. First description of eosinophilic esophagitis using confocal laser endomicroscopy (with video). *Endoscopy* 2011; **43** Suppl 2 UCTN: E66
34 **Genevay M**, Rubbia-Brandt L, Rougemont AL. Do eosinophil numbers differentiate eosinophilic esophagitis from gastroesophageal reflux disease? *Arch Pathol Lab Med* 2010; **134**: 815-825
35 **Shah A**, Kagalwalla AF, Gonsalves N, Melin-Aldana H, Li BU, Hirano I. Histopathologic variability in children with eosinophilic esophagitis. *Am J Gastroenterol* 2009; **104**: 716-721
36 **Lucendo AJ**, Friginal-Ruiz AB, Rodríguez B. Boerhaave's syndrome as the primary manifestation of adult eosinophilic esophagitis. Two case reports and a review of the literature. *Dis Esophagus* 2011; **24**: E11-E15
37 **Blanchard C**, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, Jameson SC, Kirby C, Konikoff MR, Collins MH, Cohen MB, Akers R, Hogan SP, Assa'ad AH, Putnam PE, Aronow BJ, Rothenberg ME. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; **116**: 536-547
38 **Furuta GT**, Straumann A. Review article: the pathogenesis and management of eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2006; **24**: 173-182
39 **Lucendo AJ**, Bellón T, Lucendo B. The role of mast cells in eosinophilic esophagitis. *Pediatr Allergy Immunol* 2009; **20**: 512-518
40 **Molina-Infante J**, Ferrando-Lamana L, Fernandez-Bermejo M, Porcel-Carreño S. Eosinophilic esophagitis in GERD patients: a clinicopathological diagnosis using proton pump inhibitors. *Am J Gastroenterol* 2009; **104**: 2856-2857
41 **González-Castillo S**, Arias A, Lucendo AJ. Treatment of eosinophilic esophagitis: how should we manage the disease? *J Clin Gastroenterol* 2010; **44**: 663-671
42 **Cortes JR**, Rivas MD, Molina-Infante J, Gonzalez-Nuñez MA, Perez-G M, Masa JF, Sanchez JF, Zamorano J. Omeprazole inhibits IL-4 and IL-13 signaling signal transducer and activator of transcription 6 activation and reduces lung inflammation in murine asthma. *J Allergy Clin Immunol* 2009; **124**: 607-10, 610.e1
43 **Zhang X**, Cheng E, Huo X, Yu C, Hormi-Carver KK, Andersen J, Spechler SJ, Souza RF. In esophageal squamous epithelial cell lines from patients with eosinophilic esophagitis (EoE), omeprazole blocks the stimulated secretion of eotaxin-3: a potential anti-inflammatory effect of omeprazole in eoe that is independent of acid inhibition. *Gastroenterology* 2010; **138**: S-122
44 **Spechler SJ**, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 2007; **102**: 1301-1306
45 **Dellon ES**, Gibbs WB, Fritchie KJ, Rubinas TC, Wilson LA, Woosley JT, Shaheen NJ. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1305-1313; quiz 1261
46 **Dohil R**, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci* 2012; **57**: 1413-1419
47 **Huang JJ**, Joh JW, Fuentebella J, Patel A, Nguyen T, Seki S, Hoyte L, Reshamwala N, Nguyen C, Quiros A, Bass D, Sibley E, Berquist W, Cox K, Kerner J, Nadeau KC. Eotaxin and FGF enhance signaling through an extracellular signal-related kinase (ERK)-dependent pathway in the pathogenesis of Eosinophilic esophagitis. *Allergy Asthma Clin Immunol* 2010; **6**: 25

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OBSERVATION

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Diagnosis of extent of early gastric cancer using flexible spectral imaging color enhancement

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Abstract

The demarcation line between the cancerous lesion and the surrounding area could be easily recognized with flexible spectral imaging color enhancement (FICE) system compared with conventional white light images. The characteristic finding of depressed-type early gastric cancer (EGC) in most cases was revealed as reddish lesions distinct from the surrounding yellowish non-cancerous area without magnification. Conventional endoscopic images provide little information regarding depressed lesions located in the tangential line, but FICE produces higher color contrast of such cancers. Histological findings in depressed area with reddish color changes show a high density of glandular structure and an apparently irregular microvessel in intervening parts between crypts, resulting in the higher color contrast of FICE image between cancer and surrounding area. Some depressed cancers are shown as whitish lesion by conventional endoscopy. FICE also can produce higher color contrast between whitish cancerous lesions and surrounding atrophic mucosa. For nearly flat cancer, FICE can produce an irregular structural pattern of cancer distinct from that of the surrounding mucosa, leading to a clear demarcation. Most elevated-type EGCs are detected easily as yellowish lesions with clearly contrasting demarcation. In some cases, a partially reddish change is accompanied on the tumor surface similar to depressed type cancer. In addition, the FICE system is quite useful for the detection of minute gastric cancer, even without magnification. These new contrasting images with the FICE system may have the potential to increase the rate of detection of gastric cancers and screen for them more effectively as well as to determine the extent of EGC.

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Key words: Early gastric cancer; Flexible spectral imaging color enhancement; Nonmagnified image; Magnified image; Endoscopic submucosal dissection

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INTRODUCTION

Modest changes in morphology and color of the mucosa are important factors for the diagnosis of early gastric cancer (EGC). The morphological characteristics of EGC include mild elevation and shallow depression of the mucosa, as well as discontinuity with surround-

ing mucosa and areas of uneven surface. For changes in color, pale redness or fading is important. However, these endoscopic features have not been sufficient to achieve an accurate diagnosis for EGC. The flexible spectral imaging color enhancement (FICE) system was developed as a selection system of the narrow band image and introduced in 2005 as a novel image-processing tool for video endoscopy[1-4]. FICE enhances the contrast of mucosal surface without the use of dyes. Additionally, FICE provides optimal band image with the same light intensity as conventional endoscope, implying that the FICE system can display clear images even without magnification. Indeed, FICE can facilitate detection of changes in EGC without magnification and confirm accurately the diagnosis of cancer with low or half magnification[5-7].

Endoscopic submucosal dissection (ESD) was developed in the past 10 years as a more reliable method of endoscopic resection than endoscopic mucosal resection (EMR)[8-10]. In Japan, ESD has now been officially approved as an endoscopic treatment for EGC, and the mainstream of therapy for EGC has shifted from EMR to ESD. However, the accurate diagnosis of extent of gastric cancer is needed to achieve complete resection by ESD. FICE is very useful for the diagnosis of extent without or with magnification.

In this report, advance in endoscopic diagnosis for the extent of EGCs will be reviewed particularly focusing on FICE images.

FICE SYSTEM AS ENDOSCOPIC DIAGNOSTIC TOOL

Instrument

FICE was developed with the aim of enhancing the capillary pattern and the pit patterns in endoscopic images. FICE technology is based on the selection of spectral transmittance with a dedicated wavelength. In contrast to narrow band imaging, in which the bandwidth of the spectral transmittance is narrowed by optical filters, FICE is based on a new spectral estimation technique that eliminates the need for optical filters. FICE takes an ordinary endoscopic image from a video processor and arithmetically processes the reflected photons to reconstitute virtual images for a choice of different wavelengths. Because the spectra of pixels are known, it is possible to perform imaging on a single wavelength. Such single-wavelength images are randomly selected, and assigned to red (R), green (G), and blue (B) to build and display an FICE-enhanced color image.

Instrument specifications and selection of a set of wavelengths

Endoscopes used with FICE system include EG-590ZW for routine and magnifying observation, EG-590WR for routine observation and EG-530 NW for transnasal observation, all of which are developed by Fujifilm Corporation (Kanagawa, Japan) for the upper gastrointestinal tract and need an electronic endoscope system (FTS4400 and 4450, Fujifilm). The EG-590ZW scope can magnify endoscopic images optically up to 135-fold[5-7] through the use of a zoom attachment. It is easy to change wavelengths in each endoscopic procedure, because the system allows selection of a setting from up to ten possible settings. Osawa *et al*[5] and Yoshizawa *et al*[6,7] at the Jichi Medical University in Japan selected the best setting that enhances the demarcation lines more strongly between cancerous lesions and surrounding areas in the case of EGC without magnification. For most cases of gastric cancer, the best images were obtained with use of a specific combination of the following three wavelengths: 470 nm for blue (B), 500 nm for green (G), and 550 nm for red (R) that also produces a brighter image of various types of gastric cancers, that is, depressed, flat and elevated type.

DETERMINATION OF EXTENT OF EGC WITH NONMAGNIFIED FICE IMAGES

Chromoendoscopy is often carried out by spraying dyes such as indigo carmine after thoroughly washing out the mucus and is useful to determine the extent of the tumor by clearer detection of the morphological feature of depressed or protruded cancerous margin. By contrast, FICE is often carried out not only by such detection of morphological feature but also higher color contrast between cancer and surrounding atrophic mucosa. Therefore, tumor margin may be easily identified in FICE images even without magnification.

The characteristic finding of depressed-type EGC in most cases was revealed as reddish lesions distinct from the surrounding yellowish non-cancerous area without magnification. Compared with conventional white light images, the demarcation line between the cancerous lesion and the surrounding area could be easily recognized with FICE system (Figure 1). Conventional endoscopic images provide little information regarding depressed lesions located in the tangential line, but FICE produces higher color contrast of such cancers, even with the small caliber-size scope for transnasal route[11] (EG 530NW) (Figure 1A and B). Histological findings in depressed area with reddish color changes show a high density of glandular structure and an apparently irregular microvessel in intervening parts between crypts. Such histological features differ from those of surrounding mucosa and may cause higher color contrast of FICE images between them.

Some depressed cancers are shown as whitish lesion by conventional endoscopy (Figure 2). FICE also can produce higher color contrast between whitish cancerous lesions and surrounding atrophic mucosa. For nearly flat cancer, FICE can produce an irregular structural pattern of cancer distinct from that of the surrounding mucosa, leading to a clear demarcation (Figure 3). On the other hand, most elevated-type EGCs are detected easily as yellowish lesions with clearly contrasting demarcation (Figure 4). In some cases, a partially reddish change is accompanied on the

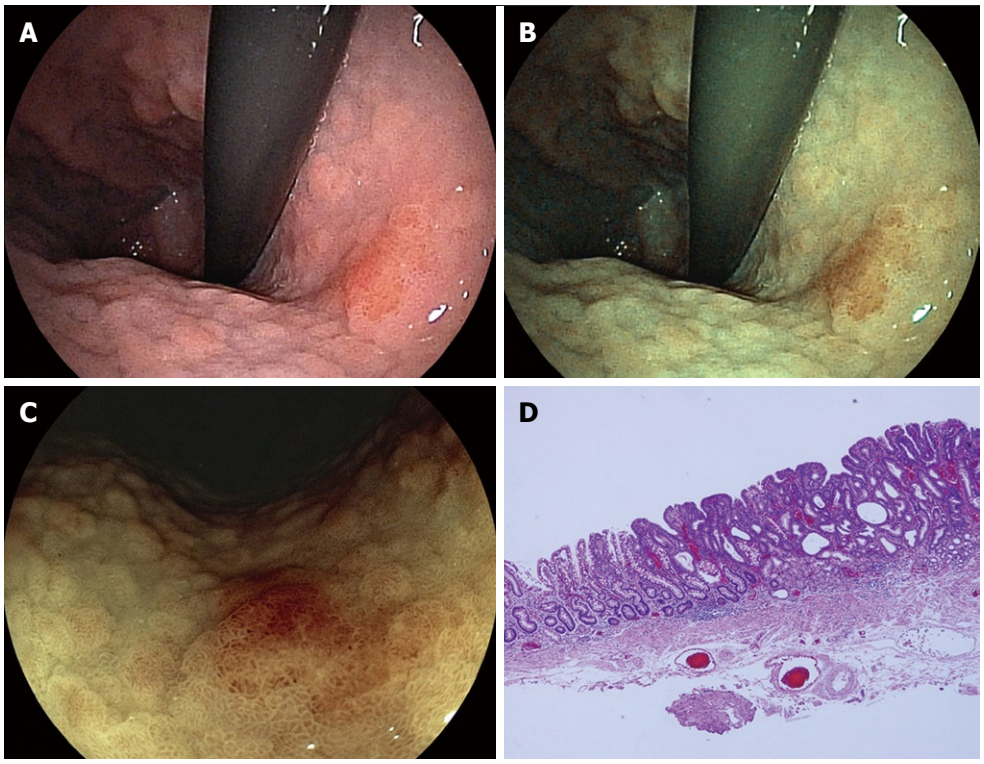

Figure 1 Image findings and specimen, A: Conventional image with small caliber endoscope (EG530-NW) reveals a slightly reddish mucosal change in the lesser curvature of the upper body; B: Flexible spectral imaging color enhancement (FICE) image with small caliber endoscope enhances a reddish cancerous lesion and can determine with precision a clear line of demarcation between cancer and the yellowish surrounding mucosa; C: FICE image with low magnification (EG590-ZW) also detects much clearer demarcation line; D: Specimen after endoscopic submucosal dissection shows a high density of glandular structure and an apparently irregular microvessel in intervening parts between crypts, which may cause a reddish mucosal change in depressed area.

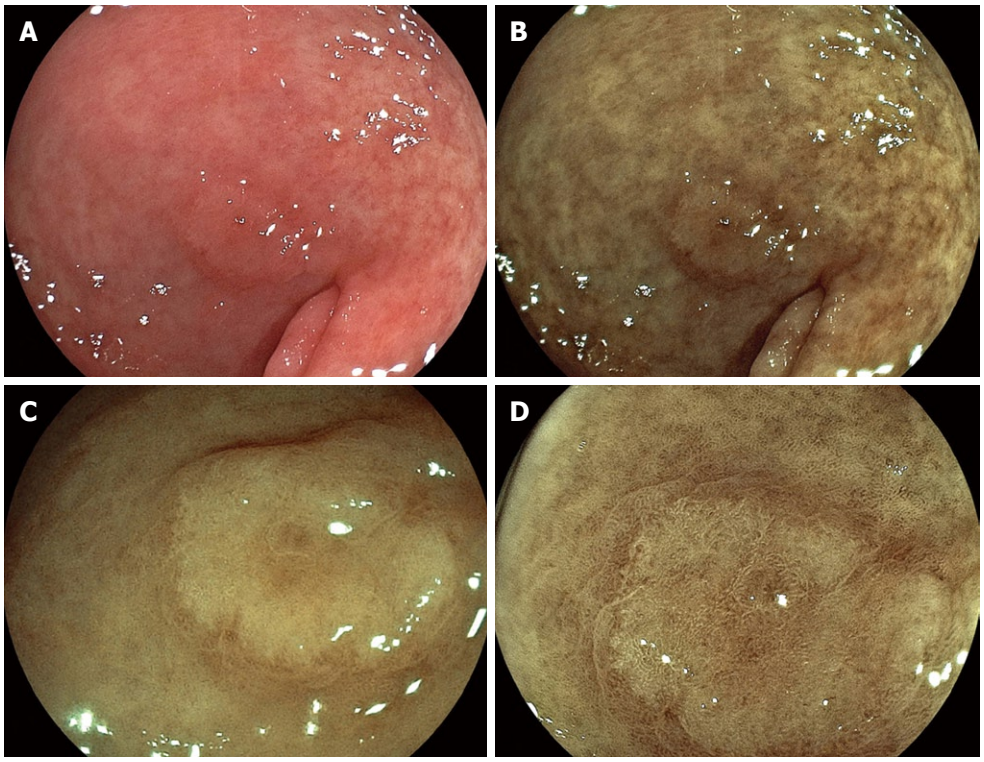

Figure 2 Some depressed cancers are shown as whitish lesion by conventional endoscopy. A: Conventional image (EG590-ZW) reveals a slightly whitish mucosal change in the anterior wall of antrum; B: Flexible spectral imaging color enhancement (FICE) image enhances a whitish cancerous lesion and can determine a line of demarcation between cancer and surrounding mucosa; C: FICE image in a close-up view (EG590-WR) detects with precision a clearer demarcation line; D: FICE image with half magnification (EG590-ZW) reveals a finer microstructural pattern on mucosal surface of cancer and higher contrasting mucosa between cancer and the surrounding area, leading a clearer demarcation line.

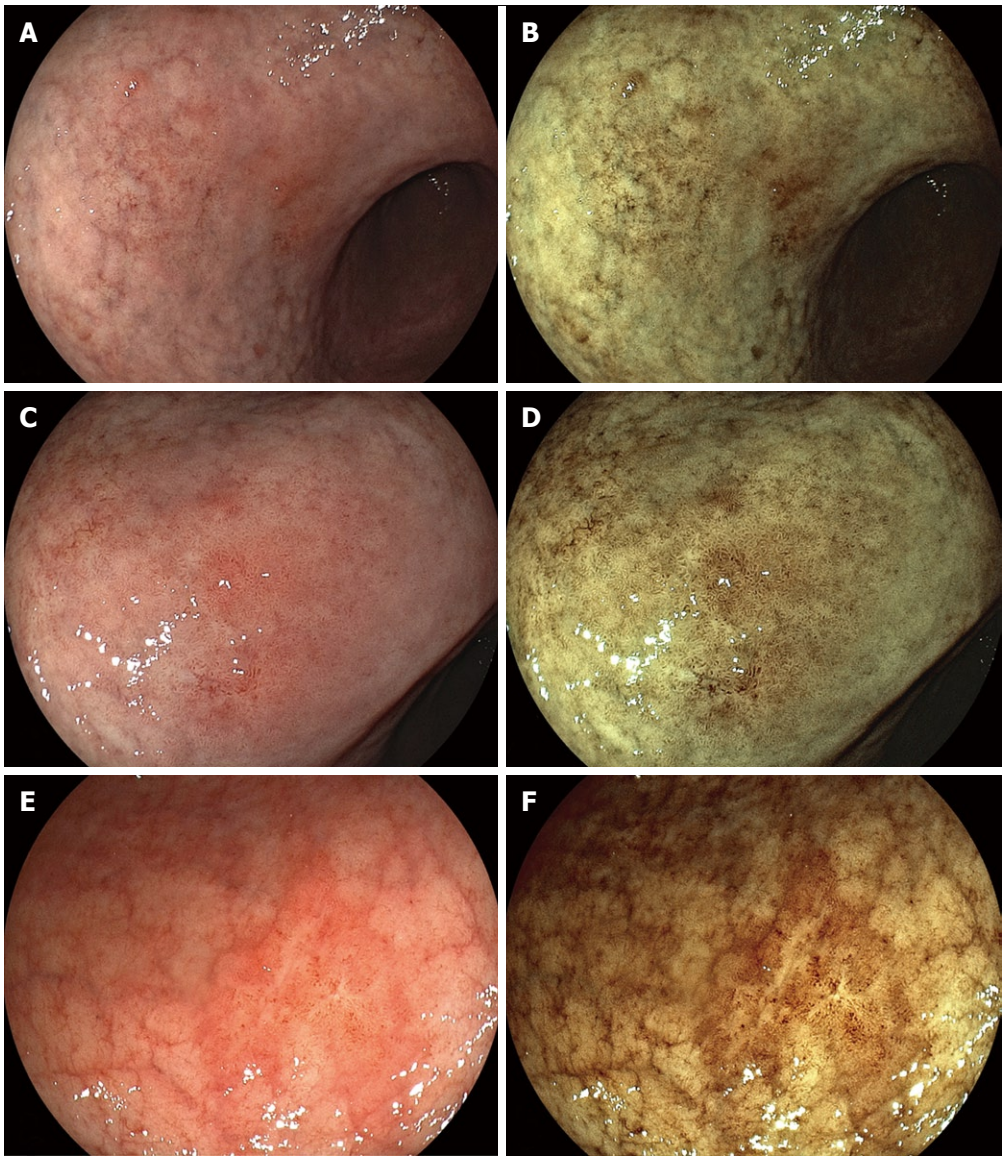

Figure 3 Conventional image and Flexible spectral imaging color enhancement image findings. A: Conventional image (EG590-ZW) reveals a slightly enriched vascular structure of gastric mucosa in the lesser curvature of the lower body; B: Flexible spectral imaging color enhancement (FICE) image enhances such a structure and shows reddish lesions in its anal side near angle; C: Conventional image near angle in a close-up view shows slightly reddish changes on the flat mucosa; D: FICE image near angle in a close-up view shows an irregular structural pattern distinct from the surrounding area, leading to a clearer demarcation line; E: Conventional image (EG590-WR) reveals a slightly enriched vascular structure in nearly flat mucosa in the antrum in a close-up view; F: FICE image enhances such a structure accompanied by a clear margin of cancer distinct from the surrounding mucosa. It is noted that these images can be obtained without magnification.

tumor surface similar to depressed type cancer (Figure 5)[5]. In addition, the FICE system is quite useful for the detection of minute gastric cancer, even without magnification. These new contrasting images with the FICE system may have the potential to increase the rate of detection of gastric cancers and screen for them more effectively as well as to determine the extent of EGC.

DETERMINATION OF THE EXTENT OF EGC WITH MAGNIFIED FICE IMAGES

Magnified FICE images are quite useful for an accurate diagnosis for EGC and determination of extent of EGC[5-7]. The irregular microstructural or nonstructural pattern is clearly identified on the tumor surface with magnification, despite the morphological types of EGC (Figures 1-4 and 6). Such patterns were found in none of the surrounding mucosa, resulting in the accurate demarcation line[5-7]. In addition, the irregular microvascular pattern of lesions is clearly visualized with half magnification (Figure 6). These findings were also helpful to confirm a definitely endoscopic diagnosis for EGC and are quite useful for marking in the noncancerous mucosa around the tumor after the determination of tumor margin, even in lesions with a blurred tumor margin by conventional images. Thus, *en-bloc* specimens with free lateral margins can be obtained by ESD. Low or half magnification in the FICE system allows endoscopists to more easily maintain the proper distance between the

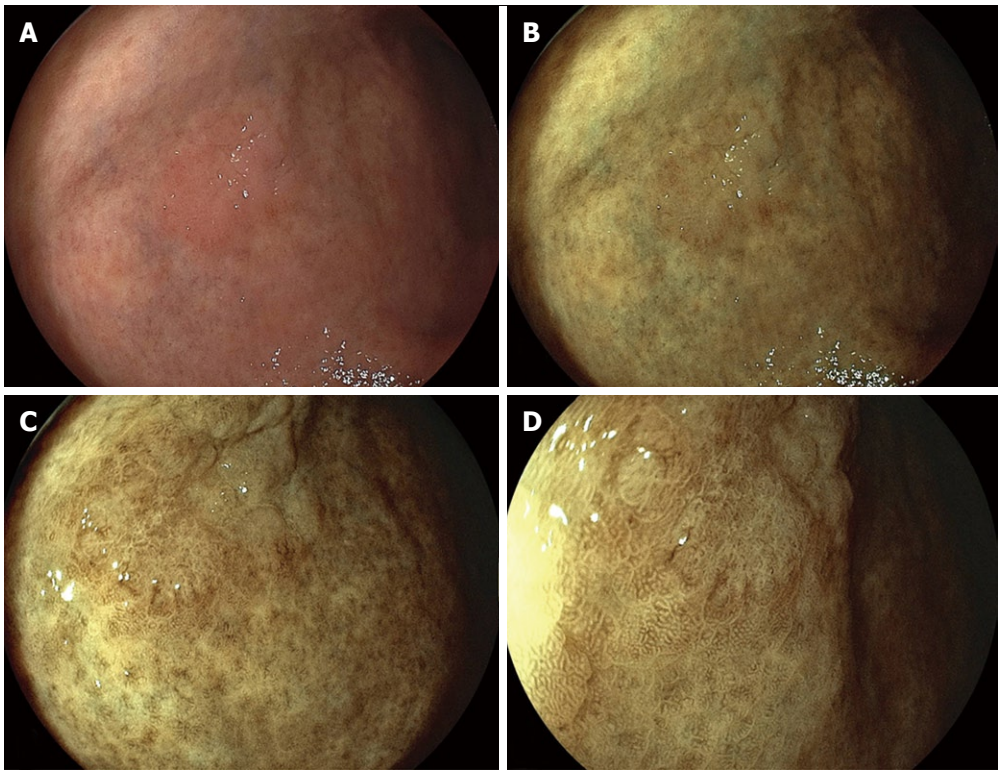

Figure 4 Most elevated-type early gastric cancers are detected easily as yellowish lesions with clearly contrasting demarcation. A: Conventional image (EG590-ZW) in a distant view reveals a slightly elevated lesion similar to the mucosal color of surrounding area in the anterior wall of lower body; B: Flexible spectral imaging color enhancement (FICE) image shows an uneven surface on the elevated tumor; C: A close-up FICE image without magnification exhibits an irregular microstructural pattern on uneven tumor surface distinct from the surrounding mucosa; D: FICE image with low magnification distinguishes an apparently irregular microstructural pattern of cancer from a normal microstructural pattern of the surrounding mucosa.

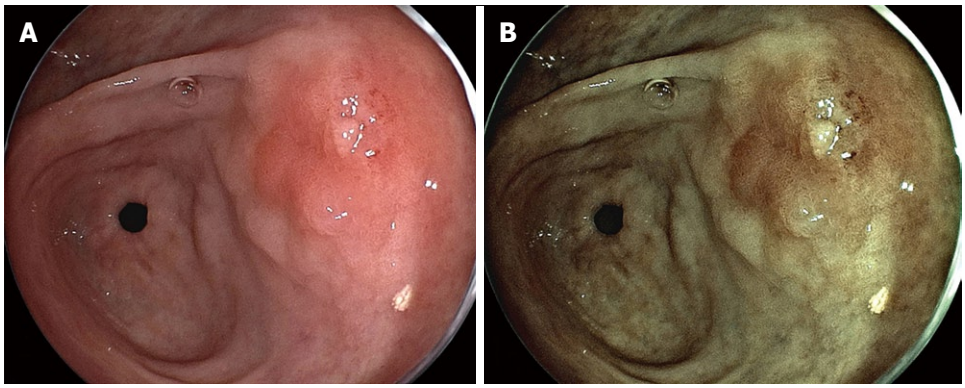

Figure 5 In some cases, a partially reddish change is accompanied on the tumor surface similar to depressed type cancer. A: Conventional image (EG590-ZW) in a distant view reveals an elevated lesion with slightly reddish portion in the posterior wall of antrum; B: Flexible spectral imaging color enhancement image enhances a reddish portion on tumor surface with more contrasting demarcation line. In addition, tumor margin of flat area in the right side of this figure can be more clearly visualized than conventional image.

tip of endoscope and the gastric mucosa and to observe broad areas that include both cancerous and surrounding noncancerous portions simultaneously on the same endoscopic images.

Histological types of gastric cancer do not influence the diagnosis of its extent and therefore an extremely high accuracy of demarcation line is maintained in most cases. However, an unclear demarcation line is evident in a few cases of EGC. The extent of gastric cancer with more than 20 mm in diameter may be misdiagnosed in a few cases even by an experienced endoscopists using FICE. Also, it is difficult to diagnose the extent of cancers with similar structural pattern to the surrounding area or accompanied by flat invasion, even though such lesions are observed with magnification.

CONCLUSION

In summary, even though targeted areas of the mucosa can be removed precisely by ESD, a complete resec-

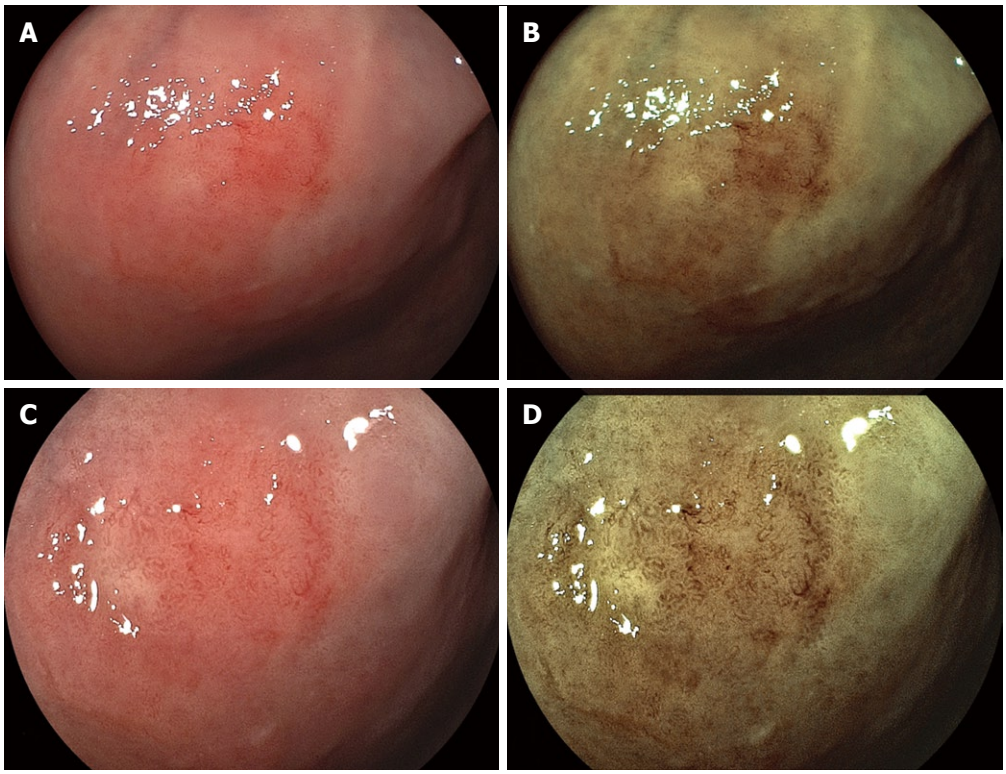

Figure 6 The irregular microvascular pattern of lesions is clearly visualized with half magnification. A: Conventional image (EG590-ZW) in a close-up view reveals a nearly flat lesion with a slightly reddish portion in the anterior wall of middle body; B: Flexible spectral imaging color enhancement (FICE) image enhances a reddish lesion leading to a clear demarcation line; C: Conventional image with half magnification shows an enriched microvascular structure on the tumor surface; D: FICE image with half magnification allows a clear visualization of irregular microvascular and microstructural pattern suggesting gastric cancer with the possible histological type of well-differentiated adenocarcinoma.

tion cannot be expected without determining the extent of EGCs. The diagnostic accuracy of extent of gastric cancer using FICE is superior to that using conventional white light image. It is noted that endoscopic diagnosis of EGC with FICE system can be performed even with non-magnified images and half magnified images. FICE can yield higher color contrast between cancerous lesion and the surrounding area and reveal an irregular structural pattern in cancerous lesions without magnification. In addition, FICE can also produce a microvascular patterns with magnification. These findings contribute to the precise determination of extent of EGC.

REFERENCES

1 **Miyake Y**, Sekiya T, Kubo S, Hara T. A new spectrophotometer for measuring the spectral reflectance of gastric mucous membrane. *J Photogr Sci* 1989; **37**: 134-138
2 **Knyrim K**, Seidlitz H, Vakil N, Classen M. Perspectives in "electronic endoscopy". Past, present and future of fibers and CCDs in medical endoscopes. *Endoscopy* 1990; **22** Suppl 1: 2-8
3 **Tsumura N**, Tanaka T, Haneishi H, Miyake Y. Optimal design of mosaic color filters for the improvement of image quality in electronic endoscopes. *Opt Commun* 1998; **145**: 27-32
4 **Haneishi H**, Shiobara T, Miyake Y. Color correction for colorimetric color reproduction in an electronic endoscope. *Opt Commun* 2003; **114**: 57-63
5 **Osawa H**, Yoshizawa M, Yamamoto H, Kita H, Satoh K, Ohnishi H, Nakano H, Wada M, Arashiro M, Tsukui M, Ido K, Sugano K. Optimal band imaging system can facilitate detection of changes in depressed-type early gastric cancer. *Gastrointest Endosc* 2008; **67**: 226-234
6 **Yoshizawa M**, Osawa H, Yamamoto H, Satoh K, Nakano H, Tsukui M, Sugano K. Newly developed optimal band imaging system for the diagnosis of early gastric cancer. *Digest Endosc* 2008; **20**: 194-197
7 **Yoshizawa M**, Osawa H, Yamamoto H, Kita H, Nakano H, Satoh K, Shigemori M, Tsukui M, Sugano K. Diagnosis of elevated-type early gastric cancers by the optimal band imaging system. *Gastrointest Endosc* 2009; **69**: 19-28
8 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942
9 **Yamamoto H**, Yahagi N, Oyama T. Mucosectomy in the colon with endoscopic submucosal dissection. *Endoscopy* 2005; **37**: 764-768
10 **Yamamoto H**. Endoscopic submucosal dissection of early cancers and large flat adenomas. *Clin Gastroenterol Hepatol* 2005; **3**: S74-S76
11 **Osawa H**, Yamamoto H, Miura Y, Ajibe H, Shinhata H, Yoshizawa M, Sunada K, Toma S, Satoh K, Sugano K. Diagnosis of depressed-type early gastric cancer using small-caliber endoscopy with flexible spectral imaging color enhancement. *Dig Endosc* 2012; **24**: 231-236

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BRIEF ARTICLE

Usefulness of the DL in ME with NBI for determining the expanded area of early-stage differentiated gastric carcinoma

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Abstract

AIM: To investigate whether magnifying endoscopy with narrow band imaging (ME-NBI) is useful for evaluating the area of superficial, depressed- or flat-type differentiated adenocarcinoma of the stomach.

METHODS: This procedure was performed in Saitama Medical University International Medical Center, Japanese Red Cross Kumamoto Hospital and Kitakyushu Municipal Medical Center. The subjects were 31 patients in whom biopsy findings, from superficial, depressed- or flat-type gastric lesion, suggested differentiated adenocarcinoma in the above 3 hospitals between January and December 2009. Biopsy was performed on the lesion and non-lesion sides of a boundary (imaginary boundary) visualized on ME-NBI. The results were pathologically investigated. We evaluated the accuracy of estimating a demarcation line (DL) on ME-NBI in comparison with biopsy findings as a gold standard.

RESULTS: The DL that could be recognized at 2 points on the orifice and anal sides of each lesion during ME-NBI was consistent with the pathological findings in 22 patients with 0-Ⅱc lesions, 7 with 0-Ⅱb lesions, and 2 with 0-Ⅱb + Ⅱc lesions, showing an accuracy of 100%.

CONCLUSION: The results suggest the usefulness of ME-NBI for evaluating the area of superficial, depressed- and flat-type differentiated adenocarcinoma of the stomach.

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Key words: Narrow band imaging; Magnifying endoscopy; Endoscopic submucosal dissection; Gastric carcinoma

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INTRODUCTION

Narrow band imaging (NBI) is a new endoscopic technique developed by Olympus Co., Ltd., which facilitates the visualization of microvascular features on the mucosal surface and their fine structure with high-level contrast employing two types of ray (central wavelengths: 415 and 540 nm, respectively)[1]. The endoscopic diagnosis of intramucosal gastric carcinoma of the superficial depressed type or flat type with nonmagnified instrument is often difficult because such carcinoma, so-called "gastritis-like cancer", are manifest as only subtle changes in color and shape. Yao *et al*[2] have reported that magnified observation without NBI of the microvascular architecture of intramucosal gastric carcinoma may be useful for characterizing flat carcinoma that exhibit only subtle changes in color and shape at standard endoscopy, and also be useful for determining the extent of intramucosal spread of differentiated carcinomas that have an irregular margin.

Yao *et al*[3] reported that a regular subepithelial capillary network (SECN) pattern was present in the mucosa around gastric carcinoma, but the pattern was lost in the microvascular architecture of differentiated gastric carcinoma, in which microvascular growth with an irregular morphology and distribution was noted, and a clear demarcation line (DL) was formed at the boundary between the cancerous and non-cancerous regions due to differences in the microvascular architecture between the regular SECN pattern and irregular microvascular pattern. However, they employed magnifying endoscopy (ME) without NBI.

Recent studies have reported that the use of NBI, which facilitates the visualization of microvascular and fine mucosal architectures, contributes to the detection of small, superficial, depressed- or flat-type adenocarcinoma of the stomach and improvement in the diagnostic capacity[4-9]. However, to date, few studies have reported the usefulness of determining of the DL of gastric cancer by ME with NBI (ME-NBI)[7,8,10,11]. In addition, according to recent studies, it is impossible to examine vascular features using this procedure in some patients with differentiated adenocarcinoma of the stomach[12,13]. When evaluating the extent of differentiated adenocarcinoma using NBI, not only differences in the microvascular architecture but also those in the fine structure of mucosa between cancerous and non-cancerous regions must be considered. Furthermore, the usefulness of ME-NBI for establishing/marking the extent of resection has been discussed. However, it is controversial to evaluate whether diagnosis of the extent of cancer using ME-NBI is accurate in a resected specimen involving a mark drawn in an area lateral to the DL visualized on ME-NBI.

Unlike the previously reported evaluation of its usefulness in endoscopic submucosal dissection (ESD) specimens[7,9-11], the present study investigated the usefulness of a new method of gastric biopsy performed during ME-NBI.

MATERIALS AND METHODS

We used magnifying endoscope (GIF-Q240Z, Olympus Optical Co., Ltd., Tokyo, Japan) combined with NBI system, consisting of an image processor (CV-260SL, Olympus), a light source (CLV-260SL, Olympus) in this study. Before the examination, a hood was mounted on the tip of the endoscope to enable the endoscopist to fix the focal distance at 2 mm between the tip of the instrument and the mucosal surface.

Thirty-one patients with superficial, differentiated carcinoma of the stomach who underwent ME-NBI in 3 hospitals (our hospital, Kitakyushu Municipal Medical Center, and Japanese Red Cross Kumamoto Hospital) between January and December 2009 were enrolled in this prospective, uncontrolled study. Examinations were carried out by 3 endoscopists specializing in NBI (1 per hospital). In all patients, the differentiated adenocarcinoma had been diagnosed previously at conventional endoscopy including biopsies with histopathologic confirmation.

Macroscopic type of the carcinoma was classified according to the classification for early stage gastric cancer of the Japanese Research Society of Gastric Cancer (Type Ⅰ, protruded; Type Ⅱa, superficial elevated; Type Ⅱb, flat; Type Ⅱc, superficial depressed; and Type Ⅲ, excavated). Carcinoma of the superficial depressed or flat types as determined at standard endoscopy were included in this study. Protruded and superficial elevated types were excluded as these are easily identified by standard endoscopy alone. Patients were excluded if the endoscopic findings using conventional endoscopy or endoscopic ultrasonography clearly suggested ulceration within the lesion, or obvious submucosal invasion, because both of these findings may influence the microvascular architecture of the lesion. In addition, we excluded patients in whom biopsy findings suggested the coexistence of undifferentiated with differentiated carcinoma.

ME-NBI was applied for 31 flat-type and superficial depressed-type lesions with unclear boundaries diagnosed as differentiated gastric carcinoma based on conventional observation and biopsy. The presence or absence of DL was judged on the oral and anal sides of the lesions. The nearest part of the lesion from the esophagogastric junction was determined by endoscopic observation and defined as oral side of the lesions. The nearest part of the lesion from the pyloric ring was also determined by endoscopic observation and defined as anal side of the lesions. Lesions with and without DL identification were presented as DL (+) and (-), respectively. Biopsy was performed, assuming regions sandwiching the DL as cancerous and non-cancerous mucosa (Figures 1 and 2).

For biopsy, we employed biopsy forceps measuring 1.8 mm in tip diameter (FB-21K-1, Olympus Tokyo). To measure the distance from the DL as objectively and accurately as possible, biopsy forceps were used as an indicator. The study used 1.8 mm biopsy forceps, the smallest commercially available, to avoid taking too much tissue and minimize the distance between two biopsy sites sandwiching the DL.

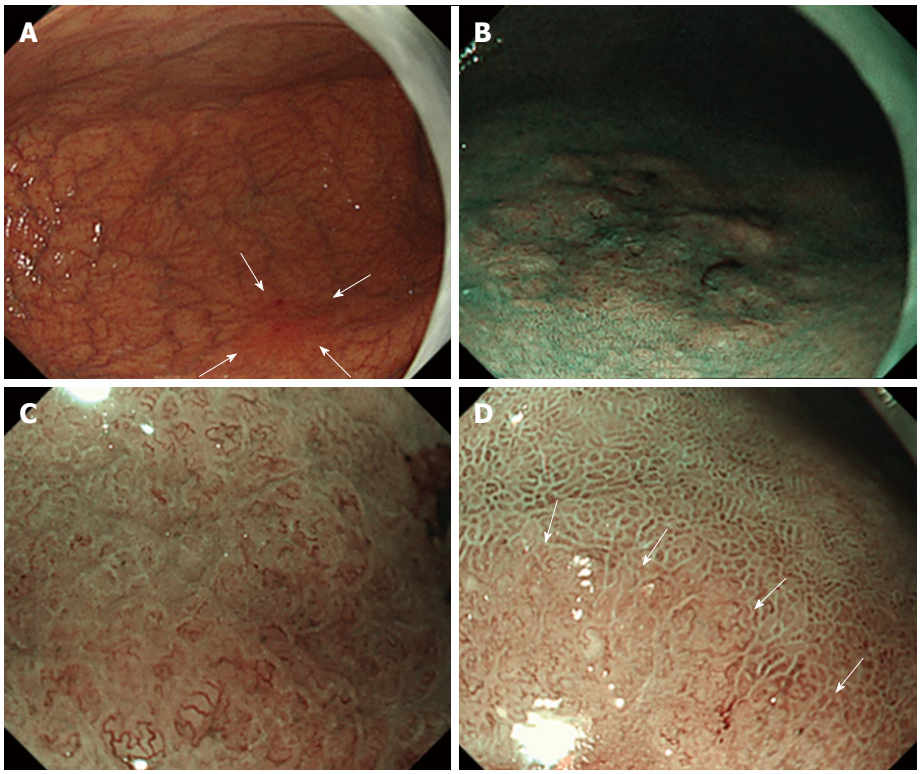

Figure 1 Narrow band imaging findings. A: Ordinary [non magnifying endoscopy with narrow band imaging (ME-NBI)] endoscopic findings of intramucosal gastric carcinoma. A flare-like flat-type (0-Ⅱb) lesion measuring 25 mm in diameter, with an unclear border, was observed at the greater curvature of the inferior gastric body (arrows); B: NBI finding of the lesion (non-ME); C: Strongly-magnified NBI finding at the lesion center; D: Moderately-magnified NBI finding at the margin: a demarcation line between the cancerous and non-cancerous regions could be recognized based on differences in the fine structure of mucosa and microvascular features (arrows). This was established as an imaginary boundary.

Establishing a distance of approximately 1.8 mm from the boundary (DL) estimated on NBI observation, two regions sandwiching it were assumed as cancerous and non-cancerous. As described above, biopsy was performed on the orifice and anal sides of each lesion. Based on the diagnostic criteria, the assistant doctor recorded the presence or absence of DL during the procedure to ensure the objectivity of the examination. The rate of consistency of the boundary between the cancerous and non-cancerous mucosa on magnified NBI and that identified in the biopsied specimen was investigated. A total of 4 biopsy specimens per lesion were collected. Therefore, 124 biopsy specimens were collected in 31 patients.

All patients gave their written informed consent. Patients who were receiving warfarin or any other anticoagulant treatment were excluded from this study. This study was approved by the Medical Ethics Committee of Saitama Medical University International Medical Center, Japanese Red Cross Kumamoto Hospital and Kitakyushu Municipal Medical Center. The UMIN Clinical Trials Registry identification number for this study is C000001769.

Statistical analysis

There is no statistical analysis. The calculations were performed by using SAS version 8.0 (SAS Institute Inc., Cary, NC).

Table 1 Clinicopathologic characteristics of patients

Age (median, yr)	71
Sex (M:F)	25:6
Location (U:M:L)	8:15:8
Tumor size (median) (range) (mm)	22 (3-72)
Macroscopic type [Ⅱb:Ⅱc:(Ⅱb + Ⅱc)]	7:22:2

The area of the lesser and greater curvatures was divided into 3. The orifice side was regarded as upper (U), intermediate area as middle (M), and anal side as lower (L). IIb: Flat type; IIc: Superficial depressed type.

RESULTS

In the 31 patients, we investigated the age, gender, lesion site, maximum diameter, morphology, presence or absence of DL at each 2 points on the orifice and anal sides, and proportion of patients in whom NBI findings were consistent with biopsy findings (Table 1). The number of patients did not reach the initial target 60, but enrollment was discontinued because the 1-year enrollment period had ended. The lesion size was measured using resected specimens. In untreated patients from whom no specimen had been resected, measuring forceps for routine observation were employed. The median age was 71 years (57-87 years). The male-to-female ratio was 25:6. Lesions were localized in the upper, middle, and lower areas in 8, 15, and 8 patients, respectively.

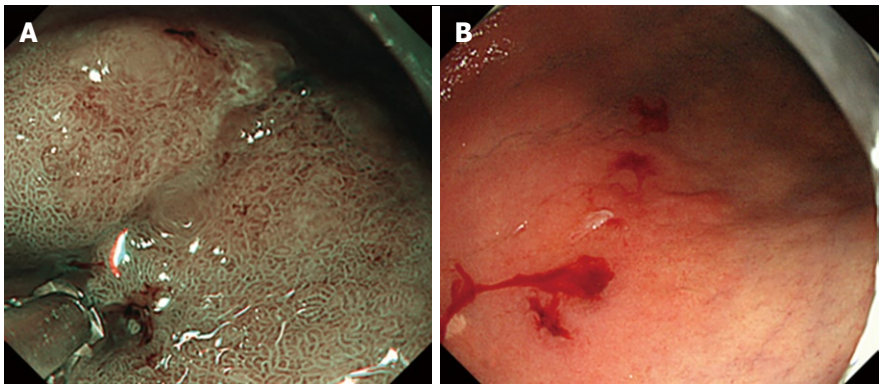

Figure 2 Biopsy findings and standard observation biopsy. A: As shown in the photograph, biopsy was performed by measuring a distance of approximately 1.8 mm using forceps (tip diameter: 1.8 mm), regarding two regions sandwiching the boundary estimated on NBI as cancerous and non-cancerous; B: Standard observation after biopsy.

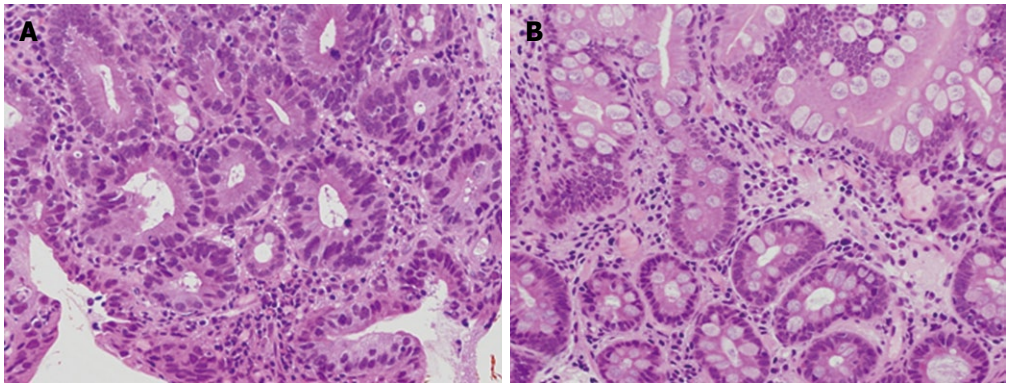

Figure 3 Pathological findings. A: HE staining of a biopsy specimen collected from the demarcation line (DL) (+) site of the patient presented in Figure 2; B: HE staining of a biopsy specimen collected from the DL (-) site of the patient presented in Figure 2.

Macroscopically, the morphology was evaluated as Ⅱb in 7 patients, Ⅱc in 22, and Ⅱb + Ⅱc in 2. The median lesion diameter was 22 mm, with an inter-quartile range of 40 mm to 14 mm. On NBI observation, the DL could be recognized at all 62 points. As shown in Figures 1 and 2, biopsy was performed, assuming two regions sandwiching the DL that could be recognized on NBI as cancerous and non-cancerous. In each 2 points in 31 patients, the imaginary boundary was consistent with a pathologically detected border between the cancerous and non-cancerous regions as a gold standard (Figure 3).

DISCUSSION

An NBI endoscopic system with 415-nm and 540-nm rays has facilitated the visualization of blood vessels in high-level contrast[1]. In this system, an incoming ray penetrates the superficial layer of translucent tissue below the mucosal epithelium, and is strongly absorbed by hemoglobin. As a secondary action, the contrast of vascular features makes it possible to evaluate the fine structure of mucosa, and an incoming ray may be strongly reflected from the mucosal surface, contributing to the visualization of its fine structure.

Based on this principle, the NBI system has commonly been employed for the diagnosis of epithelial and non-epithelial tumors of the digestive tract[12,14-17]. Previous studies involving gastric cancer patients have reported a vascular pattern (fine network pattern) specific to differentiated adenocarcinoma and a corkscrew pattern specific to undifferentiated carcinoma, employing NBI-combined magnified endoscopy. This procedure is routinely used in clinical practice. With respect to fine mucosal structures, Uedo *et al*[18] proposed a "light blue crest", Yao *et al*[12] a "white opaque substance". Diagnoses are made based on microvascular features and these mucosal structures.

Despite the widespread use of NBI, few studies to date have reported the usefulness of ME-NBI for determining the extent of gastric cancer[7,9-11]. In Japan, the widespread use of ESD has facilitated resection regardless of the tumor size in patients with early gastric cancer[19,20]. Therefore, it is very important to evaluate the extention of the lesions. Kiyotoki *et al*[11] compared ME-NBI and indigo carmine chromoendoscopy without magnification to determine the gastric tumor margin, and found that the diagnostic accuracy of the former technique was significantly higher, at 97.4%, than that of the latter, at 77.8% ($P = 0.009$). Their study included 13 patients with adenoma, in only one of whom the extent of tumor invasion by ME-NBI was misdiagnosed. As we previously reported[21], gastric adenoma differs from gastric carcinoma in that, in many cases, microvessels cannot be visualized by NBI,

or only microvessels similar to those of the surrounding mucosa can be observed and the mucosal microstructure is very difficult to distinguish from intestinal metaplasia in the surrounding gastric mucosa. Kiyotoki *et al*[11] considered that these features of gastric adenoma led to the misdiagnosis of the adenoma patient. However, the diagnostic accuracy of ME-NBI in 38 gastric cancer patients was 100%, which was similar to our results.

In a study by Kadowaki *et al*[10], a group of eight experts and a group of eight non-experts compared the usefulness of four different methods: conventional ME (CME), NE-MBI, enhanced-ME with acetic acid (EME), and ME with NBI and acetic acid (NBI-EME), for determining the extent of gastric cancer using the original scoring system. Both groups found that ME-NBI and NBI-EME were more useful for the diagnosis of the extent of gastric cancer than CME, suggesting that NE-MBI is useful even for non-experts in the diagnosis of gastric cancer invasion.

These two studies were problematic in that they did not include patients with 0-Ⅱb lesions, the extent of which is the most difficult to determine among gastric cancers, but included many with elevated lesions, the margins of which are relatively easily recognizable during routine observation. Yao *et al*[2] considered that lesions in which it is difficult to determine their extent by routine observation were superficial depressed- (0-Ⅱc) and flat-type (0-Ⅱb) gastric carcinomas (so-called "gastritis-like cancer"), performed magnified observation of these lesions without NBI, and reported the results using the expression "demarcation line". Based on this first report, we examined patients with 0-Ⅱc or 0-Ⅱb lesions. Although the present study was limited to patients with Ⅱb (flat-type) or Ⅱc (superficial depressed-type) lesions, the diagnostic accuracy for determining the cancer extent was as high as 100%.

Physicians must recognize the limitations of determining the extent of undifferentiated carcinoma, which may extend at the middle part of the lamina propria, showing no abnormal findings in the superficial mucosal layer, as well as the absence of evidence regarding the consistency between NBI-recognized and pathological boundaries in differentiated carcinoma patients who have undergone ESD involving a 2- or 3-mm marginal region *via* marking at points 2- or 3-mm lateral to the boundary estimated on NBI. In this study, to overcome these limitations, we examined the usefulness of diagnosing the extent using NBI in reference to biopsy findings as a gold standard.

According to Yao *et al*[2], when employing novel ME without NBI, the DL can be recognized based on differences in microvascular features between the cancerous and non-cancerous regions in patients with differentiated adenocarcinoma of the stomach. Araki *et al*[22] analyzed NBI-combined ME images of differentiated adenocarcinoma of the stomach using a computer. There were no significant differences in the density or mean diameter of microvessels between the cancerous and non-cancerous regions. However, branching and fusion were significantly more marked in the cancerous region. Therefore, they reported that ME-NBI was useful for evaluating the border between the cancerous and non-cancerous regions. However, actually, it is difficult to recognize microvascular features in some patients. Ezoe *et al*[13] indicated that there was no abnormal blood vessel in 17% of patients with gastric small depressive cancer. In their study described above, patients in whom no abnormal blood vessel was visually detected were also excluded[22].

ME-NBI has facilitated the visualization of microvascular features and fine mucosal structures, making it possible to recognize a boundary based on differences in the fine structure of mucosa between cancerous and non-cancerous regions. For diagnosis of the extent using NBI, it is important to initially recognize marked vascular abnormalities or those in the fine structure of mucosa at the lesion center and expand the extent of observation toward the lateral side.

In this study, we reviewed serial cases over 1 year, and the results suggested the usefulness of boundary diagnosis using NBI. However, the number of patients was small, and the 3 endoscopists participating in this study were familiar with NBI diagnosis. In the future, a larger number of patients should be investigated, and the results of this procedure carried out by beginners must be reviewed. However, taken together with the report of Kiyotoki *et al*[11], we can conclude that diagnosis of the extent using NBI is as useful as or more useful than conventional diagnosis based on standard observation. In hospitals in which 4-point biopsy has been performed to evaluate the extension of the lesion, the introduction of this method may eliminate unnecessary biopsy. In our series, biopsy led to a diagnosis of cancer before DL assessment. However, Yao *et al*[3] reported that 25.3% of patients with gastritis showed a DL on magnifying WLI. Ezoe *et al*[13] indicated DL presence on magnifying NBI in 42% of patients with non-cancerous gastric small depressive lesions. Their findings must be considered. Briefly, ME-NBI may be very useful for evaluating the extent of differentiated adenocarcinoma, but may not become an absolute diagnostic criterion for cancer.

COMMENTS

Background

Recent studies have reported that the use of narrow band imaging (NBI), which facilitates the visualization of microvascular and fine mucosal architectures, contributes to the detection of small, superficial, depressed- or flat-type adenocarcinoma of the stomach and improvement in the diagnostic capacity.

Research frontiers

There have been few studies reported the usefulness of determining of the demarcation line (DL) of gastric cancer by magnifying endoscopy with NBI (ME-NBI).

Innovations and breakthroughs

Previous studies have shown the usefulness of ME-NBI for determination of the range of early gastric cancer. However, in each study, endoscopic submucosal dissection (ESD) specimens were used for evaluation. The authors consider it difficult to discuss the usefulness of this method using ESD specimens obtained by marking a few mm outside the line recognized as the lesion border and incision a few mm outside the marking. This problem could be overcome in the present study.

Applications
In hospitals in which 4-point biopsy has been performed to evaluate the extention of the lesion, the introduction of this method may eliminate unnecessary biopsy.

Terminology
DL was formed at the boundary between the cancerous and non-cancerous regions due to differences in the microvascular architecture between the regular subepithelial capillary network pattern and irregular microvascular pattern.

Peer review
The authors prospectively studied usefulness of ME-NBI on diagnosis of differentiated early stage of gastric adenocarcinoma. This is a very interesting and novel topic. Information of this study is very important for future progress of gastrointestinal endoscopy field.

REFERENCES

1 **Gono K**, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9**: 568-577
2 **Yao K**, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest Endosc* 2002; **56**: 279-284
3 **Yao K**, Matsui T, Iwashita A. [Clinical application of magnification endoscopy with NBI for diagnosis of early gastric cancer]. *Nihon Shokakibyo Gakkai Zasshi* 2007; **104**: 782-789
4 **Ang TL**, Fock KM, Teo EK, Tan J, Poh CH, Ong J, Ang D. The diagnostic utility of narrow band imaging magnifying endoscopy in clinical practice in a population with intermediate gastric cancer risk. *Eur J Gastroenterol Hepatol* 2012; **24**: 362-367
5 **Zhang J**, Guo SB, Duan ZJ. Application of magnifying narrow-band imaging endoscopy for diagnosis of early gastric cancer and precancerous lesion. *BMC Gastroenterol* 2011; **11**: 135
6 **Ezoe Y**, Muto M, Uedo N, Doyama H, Yao K, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Takeuchi Y, Kaneko Y, Saito Y. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. *Gastroenterology* 2011; **141**: 2017-2025.e3
7 **Hirasawa D**, Fujita N, Yamagata T, Suzuki T, Noda Y. A case of early gastric cancer in which the degree of histological atypia was correctly predicted by magnifying endoscopy combined with narrow band imaging. *Dig Endosc* 2011; **23** Suppl 1: 92-94
8 **Morita Y**, Fujiwara S, Tanaka S, Toyonaga T, Azuma T. A case of small early gastric cancer that was successfully detected by narrow band imaging magnifying endoscopy. *Dig Endosc* 2011; **23** Suppl 1: 89-91
9 **Takeuchi M**, Kobayashi M, Hashimoto S, Narisawa R, Aoyagi Y. Usefulness of magnifying narrow band imaging for assessing lateral tumor extent of early gastric cancer: a case report. *Dig Endosc* 2011; **23** Suppl 1: 86-88
10 **Kadowaki S**, Tanaka K, Toyoda H, Kosaka R, Imoto I, Hamada Y, Katsurahara M, Inoue H, Aoki M, Noda T, Yamada T, Takei Y, Katayama N. Ease of early gastric cancer demarcation recognition: a comparison of four magnifying endoscopy methods. *J Gastroenterol Hepatol* 2009; **24**: 1625-1630
11 **Kiyotoki S**, Nishikawa J, Satake M, Fukagawa Y, Shirai Y, Hamabe K, Saito M, Okamoto T, Sakaida I. Usefulness of magnifying endoscopy with narrow-band imaging for determining gastric tumor margin. *J Gastroenterol Hepatol* 2010; **25**: 1636-1641
12 **Yao K**, Iwashita A, Tanabe H, Nishimata N, Nagahama T, Maki S, Takaki Y, Hirai F, Hisabe T, Nishimura T, Matsui T. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. *Gastrointest Endosc* 2008; **68**: 574-580
13 **Ezoe Y**, Muto M, Horimatsu T, Minashi K, Yano T, Sano Y, Chiba T, Ohtsu A. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. *Gastrointest Endosc* 2010; **71**: 477-484
14 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010; **28**: 1566-1572
15 **Sano Y**, Ikematsu H, Fu KI, Emura F, Katagiri A, Horimatsu T, Kaneko K, Soetikno R, Yoshida S. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**: 278-283
16 **Nonaka K**, Ishikawa K, Shimizu M, Sakurai T, Nakai Y, Nakao M, Yoshino K, Arai S, Kita H. Education and Imaging. Gastrointestinal: gastric mucosa-associated lymphoma presented with unique vascular features on magnified endoscopy combined with narrow-band imaging. *J Gastroenterol Hepatol* 2009; **24**: 1697
17 **Nonaka K**, Ishikawa K, Arai S, Shimizu M, Sakurai T, Nishimura M, Nakao M, Sasaki Y, Kita H. Magnifying endoscopic observation of mantle cell lymphoma in the stomach using the narrow-band imaging system. *Endoscopy* 2010; **42** Suppl 2: E94-E95
18 **Uedo N**, Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T, Imanaka K, Takeuchi Y, Higashino K, Ishiguro S, Tatsuta M. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006; **38**: 819-824
19 **Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928
20 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942
21 **Nonaka K**, Arai S, Ban S, Kitada H, Namoto M, Nagata K, Ochiai Y, Togawa O, Nakao M, Nishimura M, Ishikawa K, Sasaki Y, Kita H. Prospective study of the evaluation of the usefulness of tumor typing by narrow band imaging for the differential diagnosis of gastric adenoma and well-differentiated adenocarcinoma. *Dig Endosc* 2011; **23**: 146-152
22 **Araki Y**, Sasaki Y, Hanabata N, Yoshimura T, Sawaya M, Hada R, Fukuda S. Morphometry for microvessels in early gastric cancer by narrow band imaging-equipped magnifying endoscopy. *Dig Endosc* 2011; **23**: 233-239

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BRIEF ARTICLE

Learning curve for double-balloon enteroscopy: Findings from an analysis of 282 procedures

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Abstract

AIM: To determine the learning curves for antegrade double-balloon enteroscopy (aDBE) and retrograde DBE (rDBE) by analyzing the technical success rates.

METHODS: A retrospective analysis in a tertiary referral center. This study reviewed all cases from June 2006 to April 2011 with a target lesion in the small-bowel identified by either capsule endoscopy or computed tomography scan posted for DBE examinations. Main outcome measurements were: (1) Technical success of aDBE defined by finding or excluding a target lesion after achieving sufficient length of small bowel intubation; and (2) Technical success for rDBE was defined by either finding the target lesion or achieving stable overtube placement in the ileum.

RESULTS: Two hundred and eighty two procedures fulfilled the inclusion criteria and were analyzed. These procedures were analyzed by blocks of 30 cases. There was no distinct learning curve for aDBE. Technical success rates for rDBE continued to rise over time, although on logistic regression analysis testing for trend, there was no significance (P = 0.09). The odds of success increased by a factor of 1.73 (95% CI: 0.93-3.22) for rDBE. For these data, it was estimated that at least 30-35 cases of rDBE under supervision were needed to achieve a good technical success of more than 75%.

CONCLUSION: There was no learning curve for aDBE. Technical success continued to increase over time for rDBE, although a learning curve could not be proven statistically. Approximately 30-35 cases of rDBE will be required for stable overtube intubation in ileum.

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Key words: Double-balloon enteroscopy; Learning curve; Credential; Training; Success rate

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INTRODUCTION

The American Society for Gastrointestinal Endoscopy has guidelines specifically addressing standards for training, assessing competence, and granting privileges to endoscopy[1]. Together with American College of Gastroenterology, quality indicators for major endoscopic procedures like esophagogastroduodenoscopy (EGD)[2], colonoscopy[3], endoscopic retrograde cholangiopancreatography (ERCP)[4] and endoscopic ultrasonography

(EUS)[5] were formulated. Efforts from numerous groups of researchers in the past in developing performance parameters contributed significantly in formulating end-points that define high quality endoscopic services.

Since the introduction of double-balloon enteroscopy (DBE) by Yamamoto *et al*[6] in 2001, the technique has developed into a widely used intervention for small bowel diagnosis and therapy. However, performance parameters in DBE are lacking. Several recent papers[7,8] had addressed some questions regarding technical success. Gross *et al*[9] evaluated the improvement in clinical impact and noted that with experience, helpful clinical impact rose. We retrospectively studied all DBE cases performed in our institution and investigate the learning curves for both ante grade and retrograde approaches with a focus on technical end-points.

MATERIALS AND METHODS

Study protocol

This is a single-center retrospective study in a tertiary referral teaching hospital in Sydney, Australia. In our institution, one endoscopist (who is the senior author of this article) with experience in DBE and in therapeutic endoscopy performed all procedures, with trainees assisting with the overtube. The endoscopist has an experience of performing approximately 10 000 EGD, 7000 colonoscopies, 4000 ERCPs and 2500 EUS. DBE was performed using the Fujinon enteroscope (Fujinon EN-450T5, Fujinon Corporation, Saitama, Japan). DBE was performed *via* the antegrade (aDBE) or retrograde (rDBE) route, and the intention was to perform a targeted approach with the DBE. The approach was determined by the endoscopist, based on the position the lesion was suspected most often determined by the time a lesion was seen in relation to the total small-bowel transit time on a capsule endoscopy (CE) study. If the lesion was within the proximal two thirds of the small-bowel, then an aDBE was used.

The DBE was performed with the patient under conscious or deep sedation with a combination of intravenous midazolam (Pfizer, Bentley, Australia), fentanyl (Mayne Pharma Ltd., Mulgrave, Australia), and propofol (Fresofol 1%, Pharmatel Fresenius Kabi Pty Ltd., Hornby, Australia) administered by the assistant or attending anesthetist. The preparation for the procedures included a fasting period of 8 h before the oral procedure and a routine bowel preparation with a sodium picosulfate–based (Picoprep, Pharmatel Fresenius Kabi Pty Ltd, Hornsby, Australia), or sodium phosphate-based preparations (Fleet, Ferring Pharmaceuticals, Gordon, Australia) with a clear fluid diet the day before the procedure for the anal approach. The technique of DBE was previously described by the innovator Yamamoto *et al*[6].

Institutional Review Board approval was obtained before data collection. Information on DBE was extracted from the endoscopy unit database. Clinical records of these patients were traced from the Medical Record Department. Information on patient demographics, indications, previous investigations (endoscopic and radiologic), findings and intervention with DBE, limitations of insertion, complication rates, and immediate follow-up after therapy were all retrieved.

Inclusion criteria

Inclusion criteria for this study were patients who had lesions suspected on CE or other imaging techniques such as computed tomography (CT), small-bowel barium meal follow-through performed prior to DBE. These lesions were used as target lesions for DBE.

Definitions of success

For aDBE: Success was defined by finding the target lesion seen on previous imaging or insertion of enteroscope beyond the suspected site of lesion as estimated on prior imaging, in such a way that it sufficiently excluded the presence of a lesion.

For rDBE: Success was defined by finding the target lesion or stable intubation into the ileum with overtube balloon securely placed beyond the ileocecal valve. This criterion was chosen since stable overtube placement in the ileum is fundamental to "anchor" the overtube above ileocecal valve and prevent frequent falling back into the cecum. This was perceived by the endoscopist by the disappearance of the resistance for advancement.

All cases included were discussed with the endoscopist, who is the senior author of this paper, to decide on their success rate based on the above pre-defined criteria.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences version 14.0 (Chicago, IL, United States). The mean ± SD, and range were calculated for continuous data. Categorical data analysis was performed by using the Fisher exact test. The analysis was performed separately for aDBE and rDBE. In each group, data was analyzed by dividing them into blocks of approximately 30 cases each. These were plotted against time. Logistic regression analysis was used to test for a trend in the proportion of successes in each block over time. Statistical analysis was also performed to evaluate the differences between the blocks of procedures. A $P < 0.05$ was considered to be statistically significant.

RESULTS

Demographics

From June 2006 to April 2011, a total of 333 procedures (204 antegrade, 129 retrograde) were performed on 268 patients. Fifty-one procedures were excluded because of no target lesions seen on previous investigations ($n = 32$), procedures performed for colonic indications ($n = 10$), poor bowel preparation ($n = 4$), sedation failure ($n = 3$) and technical/equipment failure ($n = 2$). Thus 282 cases were analyzed (184 antegrade, 98 retrograde). The mean ± SD age was 62 (18) years and 152 patients were female (53.9%).

Table 1 Target lesions from previous investigations prior to double-balloon enteroscopy

Modalities of investigation	Target lesions	*n*
Capsule endoscopy (total = 269)	Vascular lesions	
	Angioectasia	100
	Red spots	9
	Neoplastic lesions	
	Mass lesions	36
	Polyps	35
	Evidence of bleeding	
	Blood	25
	Other lesions	
	Ulcers	23
	Erosions	6
	Mucosal abnormality	5
	Enteritis	4
	Strictures	4
	Double pathology	
	Angioectasia and polyps	9
	Angioectasia and ulcers	5
	Angioectasia and erosions	3
	Angioectasia and mass lesions	2
	Angioectasia and stricture	2
	Blood and mass lesion	1
CT scan (total = 13)	Thickened small bowel	8
	Mass lesions	5

CT: Computed tomography.

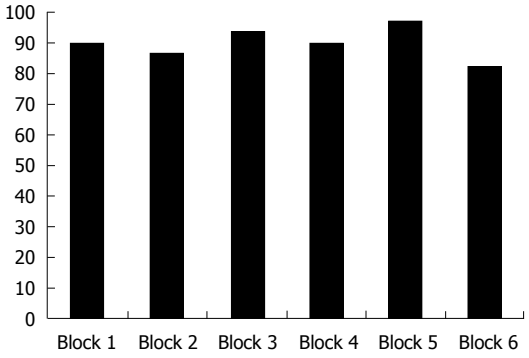

Figure 1 Bar chart showing technical success rates in antegrade double-balloon enteroscopy (184 cases analyzed in blocks of 30, 30, 30, 30, 30, 34).

Target lesions

The target lesion was identified by either CE (95.4%) or CT scan (4.6%). The target lesions and their modalities of investigations were summarized in Table 1. Angioectasia was the most common target lesion and was the target lesion in 121 (42.9%) procedures, followed by small-bowel polyps in 44 (15.6%) procedures.

Technical success

For aDBE: The overall technical success for the aDBE cohort was 89.7% (165/184). The technical success rates of aDBE were analyzed by 6 blocks of 30/30/30/30/30/34. The results are shown in Table 2 and Figure 1. The first 30 cases demonstrated a success of 90.0% and remained consistent throughout. There is no statistically significant improvement with increasing experience as logistic regression analysis testing for trend over time was not significant ($P = 0.73$).

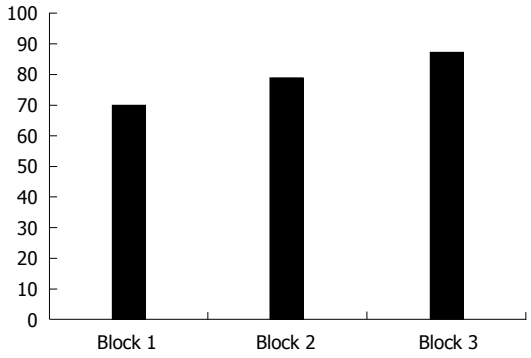

Figure 2 Bar chart showing technical success rates in retrograde double-balloon enteroscopy (98 cases analyzed in blocks of 33, 33, 32).

For rDBE: The overall technical success for the rDBE cohort was 78.6% (77/98). The technical success rates of aDBE were analyzed by 3 blocks of 33/33/32. Success according to increasing experience is shown in Table 3 and Figure 2. The initial success on first block was 70% but increased to 78.8% and 87.5% in subsequent blocks. There was no statistical significance when the second and third blocks were compared to the first block ($P = 0.40$ and 0.09). Logistic regression analysis testing for trend over time also did not show significance ($P = 0.09$).

Complication

One patient with ongoing small bowel bleeding from an angioectasia in the distal small bowel underwent a retrograde procedure with diathermy of the lesion presented 2 d later with a bowel perforation. He subsequently had a laparotomy and found a bowel perforation at the diathermy site. Resection and re-anastomosis were done and patient recovered well.

DISCUSSION

Endoscopic procedures have evolved over the years with new emerging techniques designed to improve the quality of imaging and interventions. Learning curves for various endoscopic procedures were defined in the past, leading to official recommendations of threshold procedure numbers that should be carried out by trainees in order to obtain competence in endoscopy. The determination of these numbers is important in order to guide the teachers and learners, allowing endoscopists to be credentialed accordingly. Available data suggest that at least 25-30 flexible sigmoidoscopies[1,10], 130 upper endoscopies[1], 140 colonoscopies[1,11], and 180-300 ERCPs[1,12,13] are required for the usual trainee to achieve competence. However, there were concerns that an arbitrary number of procedures do not guarantee competency[14-16] and different levels of competency are required for different clinical endpoints desired. For example, pancreatobiliary EUS demands more experience than esophageal EUS[17],

Table 2 Analysis of 184 cases of antegrade double-balloon enteroscopy with regards to technical success rate (divided into 6 blocks of 30, 30, 30, 30, 30, 34 cases)

Block No.	Details on outcome			Cases classified as clinical success (a+b)	Success rate (%)	P^1
	Target lesions found (a)	Target lesions excluded (b)	Failed (c)			
1 (n = 30)	18	9	3	27/30	90.0	0.73
2 (n = 30)	20	6	4	26/30	86.7	
3 (n = 30)	18	10	2	28/30	93.3	
4 (n = 30)	17	10	3	27/30	90.0	
5 (n = 30)	17	12	1	29/30	96.7	
6 (n = 34)	16	12	6	28/34	82.4	

[1]Logistic regression analysis testing for trend over time. Overall success rate: 165/184 = 89.7%.

Table 3 Analysis of 98 cases of retrograde double-balloon enteroscopy with regard to technical success rate (divided into 3 blocks of 33, 33, 32 cases)

Block No.	Cases classified as technical success (finding the target lesion and/or stable overtube intubation in ileum)	Success rate (%)	P^1
1 (n = 33)	23/33	70.0	0.09
2 (n = 33)	26/33	78.8	
3 (n = 32)	28/32	87.5	

[1]Logistic regression analysis testing for trend over time. Overall success rate: 77/98 = 78.6%.

while 40-50 cases may provide adequate preparation for the accurate evaluation of submucosal lesions.

In considering such recommendations, we must first define expert or experienced levels of success to help define what should be the benchmark for others particularly in the accreditation of training competency. Two aspects in defining the success of any procedure are the identification of a performance standard and defining an acceptable level of success. For instance, in ERCP, cannulation and opacification of desired duct can be considered the performance standard and 80% success rate is the minimum measure of competency[18].

To date, there is little evidence defining performance parameters and describing the benchmark success level for DBE. Mehdizadeh *et al*[7,8] analyzed initial experience in 6 United States centers with regards to the learning curve of the procedure based on technical parameters like examination duration, depth of insertion, findings and technical success. The same group concluded that there was a significant decline in overall procedural and fluoroscopy times after the initial 10 DBE cases[7]. Also, 20 cases were taken as the minimum number for retrograde procedures to attain certain level of competency[8]. The only other article addressing the learning curve of DBE studied the clinical impact of DBE. In this case, Gross *et al*[9] demonstrated a rise of clinically helpful procedures from 58% to 86% comparing the first and last 50 procedures in a 200 DBE series.

The technical success of a procedure is usually based upon attainment of certain anatomical landmarks such as the cecum in colonoscopy. Due to little or no differentiation in the proximal small-bowel, definition of the technical success was not very useful for antegrade procedures. For retrograde procedures, finding the target lesion and/or stable overtube intubation of the ileum were chosen to be the definition of technical success in this study. Stable overtube intubation beyond ileocecal valve prevents retrograde movement of the system into the cecum, a key point in allowing the advancement of the enteroscope more proximally. This landmark was taken as the division between a successful and a failed procedure technically, a view previously acknowledged by Mehdizabeh *et al*[8]. In our series the overall technical success was 78.6% in the retrograde procedures, which is similar to Mehdizabeh's observation of a failure to intubate small-bowel in 21%-31%[7,8].

Our series indicates that an endoscopist experienced in standard endoscopy may be able to perform aDBE with limited training, a view shared by Gross *et al*[9]. With regards to retrograde procedures, there was a gradual improvement for better technical success over time, although this was not statistically significant on trend analysis. A minimum of 30-35 cases in our series were needed in order to achieve more than 75% technical success. With this we will have a suitable platform to measure acceptable levels of success in DBE and provide meaningful recommendations for future trainees. The current literature including our work touches on some of these key issues and some patterns are developing but no clear recommendations can be made for training at this point. The study showed a trend towards technical success over time for rDBE as compared to aDBE. This could be due to the technical complexity of the retrograde approach, as compared to rather featureless anatomical structure of upper small bowel. These differences translate to some sort of learning curve as reflected by a trend towards technical success over time for rDBE.

We recognized several limitations with this study. Being a retrospective series, we are subject to reporting and interpretation bias. In addition, the endpoints measured are subject to interpretation and as confidence built during our experience this could have led to the perceived increase in success. We acknowledged that the definition for technical success in antegrade procedures in this study may be subjective due to lack of distinct anatomical

landmark in the upper small-bowel. In addition, a single operator/center experience limits our ability to widely apply these results.

In conclusion, there seems to be no learning curve for aDBE. However, a gradual increase of successful retrograde procedures was noted with ongoing experience. Our study indicated a minimum of 30-35 cases of retrograde procedures were required to achieve stable ileal intubation and meaningful endoscopic success. Further larger studies will be required to define technical and clinical endpoints and to measure acceptable levels of success in DBE.

COMMENTS

Background

This study investigated the learning curve of double-balloon-enteroscopy (DBE) based on certain predefined criteria as successful endpoints.

Research frontiers

This is a not well-studied topic as current know-how on DBE is still lacking. Literatures on learning curve of the procedure are sparse as difficulties often encountered on definition of success in this procedure.

Innovations and breakthroughs

The paper used certain endpoints as technical success of the procedure. This is the first time these criteria were used to define the success of performing DBE.

Applications

This is an important area as it allows future policy-makers to determine number of cases required prior to attainment of competency in performing DBE. DBE is expected to find more applications clinically and knowledge on learning curve will allow an appropriate credentialing for the procedurists.

Terminology

Antegrade DBE is used to imply DBE that uses an antegrade approach as compared to retrograde DBE which means the retrograde approach.

Peer review

The reviewers appreciated that this is an interesting area whereby data are lacking and a good study is difficult. Despite the fact that this study is a single-operator experience, it has its value in providing reference in quality control of procedures.

REFERENCES

1 **Eisen GM**, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, Mallery JS, Raddawi HM, Vargo JJ, Waring JP, Fanelli RD, Wheeler-Harbough J. Methods of granting hospital privileges to perform gastrointestinal endoscopy. *Gastrointest Endosc* 2002; **55**: 780-783

2 **Cohen J**, Safdi MA, Deal SE, Baron TH, Chak A, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Petrini JL, Rex DK, Faigel DO, Pike IM. Quality indicators for esophagogastroduodenoscopy. *Am J Gastroenterol* 2006; **101**: 886-891

3 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885

4 **Baron TH**, Petersen BT, Mergener K, Chak A, Cohen J, Deal SE, Hoffinan B, Jacobson BC, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic retrograde cholangiopancreatography. *Am J Gastroenterol* 2006; **101**: 892-897

5 **Jacobson BC**, Chak A, Hoffman B, Baron TH, Cohen J, Deal SE, Mergener K, Petersen BT, Petrini JL, Safdi MA, Faigel DO, Pike IM. Quality indicators for endoscopic ultrasonography. *Am J Gastroenterol* 2006; **101**: 898-901

6 **Yamamoto H**, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K. Total enteroscopy with a nonsurgical steerable double-balloon method. *Gastrointest Endosc* 2001; **53**: 216-220

7 **Mehdizadeh S**, Ross A, Gerson L, Leighton J, Chen A, Schembre D, Chen G, Semrad C, Kamal A, Harrison EM, Binmoeller K, Waxman I, Kozarek R, Lo SK. What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. *Gastrointest Endosc* 2006; **64**: 740-750

8 **Mehdizadeh S**, Han NJ, Cheng DW, Chen GC, Lo SK. Success rate of retrograde double-balloon enteroscopy. *Gastrointest Endosc* 2007; **65**: 633-639

9 **Gross SA**, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. center. *Gastrointest Endosc* 2008; **67**: 890-897

10 **Hawes R**, Lehman GA, Hast J, O'Connor KW, Crabb DW, Lui A, Christiansen PA. Training resident physicians in fiberoptic sigmoidoscopy. How many supervised examinations are required to achieve competence? *Am J Med* 1986; **80**: 465-470

11 **Cass OW**, Freeman ML, Cohen J, Zuckerman G, Watkins J, Nord J, Locke GR, Jensen D, Diehl D, Cerulli M, Lyche K, Fennerty M, Edmundowicz S, Etzkorn K, Al-Kawas F, Cave D, Lehman G. Acquisition of competency in endoscopic skills (ACES) during training: A multicenter study. *Gastrointest Endosc* 1996; **43**: 308A

12 **Jowell PS**, Baillie J, Branch MS, Affronti J, Browning CL, Bute BP. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. *Ann Intern Med* 1996; **125**: 983-989

13 **Verma D**, Gostout CJ, Petersen BT, Levy MJ, Baron TH, Adler DG. Establishing a true assessment of endoscopic competence in ERCP during training and beyond: a single-operator learning curve for deep biliary cannulation in patients with native papillary anatomy. *Gastrointest Endosc* 2007; **65**: 394-400

14 **Cass OW**, Freeman ML, Peine CJ, Zera RT, Onstad GR. Objective evaluation of endoscopy skills during training. *Ann Intern Med* 1993; **118**: 40-44

15 **Friedman LS**. How long does it take to learn endoscopy? *Gastrointest Endosc* 1995; **42**: 371-373

16 **Marshall JB**. Technical proficiency of trainees performing colonoscopy: a learning curve. *Gastrointest Endosc* 1995; **42**: 287-291

17 **Hoffman BJ**, Hawes RH. Endoscopic ultrasound and clinical competence. *Gastrointest Endosc Clin N Am* 1995; **5**: 879-884

18 Training the gastroenterologist of the future: the gastroenterology core curriculum. The Gastroenterology Leadership Council. *Gastroenterology* 1996; **110**: 1266-1300

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CASE REPORT

A case of EMRC for basaloid squamous carcinoma of the cervical esophagus

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Abstract

Basaloid squamous carcinoma (BSC) of the esophagus is a rare esophageal tumor. A 79-year-old man with a history of proximal gastrectomy for gastric adenocarcinoma in 2000 was followed-up by esophagogastroduodenoscopy (EGD) annually. In June 2010, EGD revealed a new protruding lesion in the cervical esophagus. The small lesion was approximately 5 mm in size. A biopsy specimen showed poorly differentiated squamous cell carcinoma. We performed endoscopic mucosal resection using a cap-fitted endoscope (EMRC). The histological diagnosis of the endoscopically resected specimen was BSC and the invasion depth was limited to the muscularis mucosae. Horizontal and vertical margins were negative. We report the case of superficial BSC in the cervical esophagus successfully resected by EMRC.

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INTRODUCTION

Basaloid squamous carcinoma (BSC) of the esophagus is a rare esophageal tumor[1]. It has been reported to have a poor prognosis because the incidences of lymph node and distant metastases are high in comparison with esophageal squamous cell carcinomas (SCCs)[2-4]. Therefore, surgical resection is generally performed for BSC. We report a case of small BSC in the cervical esophagus treated by endoscopic mucosal resection (EMR) using a cap-fitted endoscope (EMRC).

CASE REPORT

The patient was a 79-year-old man with a history of proximal gastrectomy due to gastric adenocarcinoma in 2000. He was annually followed-up by esophagogastroduodenoscopy (EGD). In June 2010, EGD revealed a new protruding lesion in the cervical esophagus. Pathological examination of an endoscopic biopsy specimen revealed poorly differentiated SCC, and he was referred

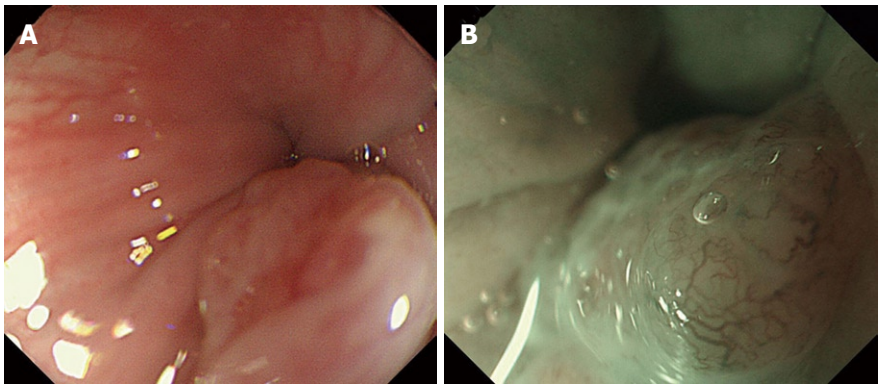

Figure 1 Endoscopic images. A: An endoscopic image shows a protruding lesion located in the cervical esophagus; B: Magnifying endoscopy with narrow-band imaging shows microvessels of type 4 M of the Arima classification.

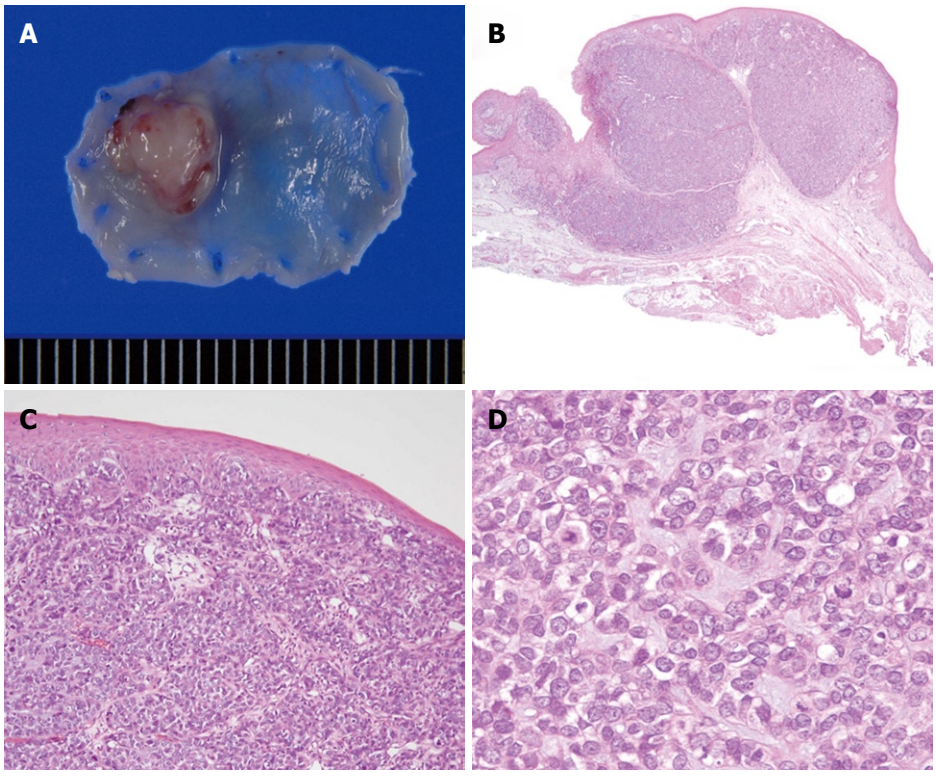

Figure 2 Resected specimen. A: In a fresh resected specimen, the lesion is defined as 0- I and measures 7 mm × 6 mm; B: The histological diagnosis is basaloid squamous carcinoma (BSC), and tumor invasion depth is limited to the muscularis mucosae (HE, × 40); C: BSC is located in the lamina propria mucosae, and covered by normal squamous epithelium (HE, × 100); D: The tumor consists of oval cells like basal cells (HE, × 200).

to our hospital for further examination and treatment. The lesion was so small that he had no symptoms such as dysphagia. Physical examination and laboratory data revealed no abnormalities with the exception of an abdominal scar from laparotomy and mild anemia (Hb 111 g/L). Chest and abdominal computed tomography scanning and abdominal ultrasonography revealed no evidence of either lymph node or distant metastasis. EGD showed a protruding lesion located in the cervical esophagus (Figure 1A). The lesion was approximately 5 mm in size, and the surface was reddish and slightly rough. Magnifying endoscopy with narrow-band imaging (ME-NBI) showed the smooth surface of the lesion, and an avascular area surrounded by irregularly branched vessels (Figure 1B). The microvascular pattern was diagnosed as type 4M of Arima's classification[5]. We diagnosed that the depth of tumor invasion was limited to the muscularis mucosae (MM) and performed EMRC with a GIF-H260Z (Olympus Corporation, Tokyo, Japan). Saline with indigocarmine was injected into the submucosa, and the lesion was lifted. The lesion was suctioned into the cap, and resected *en bloc* with the prelooped snare. There were no complications such as bleeding or perforation.

We show an image of the resected specimen in Figure 2A. The lesion was defined as 0- I (protruding type) according to endoscopic classification based on the Guide-

lines for Clinical and Pathologic Studies of the Japanese Society for Esophageal Disease[6]. The size of the lesion was 7 mm × 6 mm. The histological diagnosis was BSC and the invasion depth was limited to the MM (Figure 2B). The lesion was mainly located in the lamina propria mucosae (LPM) and covered with normal squamous epithelium (Figure 2C). The lesion consisted of oval cells like basal cells (Figure 2D). Horizontal and vertical margins were negative for cancer cells, and neither lymphatic nor venous invasion was observed. We followed the patient up without recurrence in the 6 mo after EMRC.

DISCUSSION

BSC of the esophagus is a rare tumor. It is reported in 0.068% of esophagectomy cases and 0.4% of autopsied cases[7]. BSC is derived from basal cells in the deepest epithelial layer and rapidly invades the LPM or deeper. Most BSC lesions reported previously in the literature invaded the muscularis propria or deeper[2-4]. In these cases, BSC was reported to have a worse prognosis than SCC of the esophagus because of the higher rates of lymph node and distant metastases[8].

Recently, it has been reported that superficial BSCs limited to within mucosal or submucosal layers have increased. Mori *et al*[9] reviewed 68 esophageal BSCs and found that the rates of lymph node metastasis were 0% (0/4) in mucosal BSCs and 21.8% (14/64) in the submucosal lesions. These results indicated that the rate of lymph node metastases of superficial BSCs did not differ from ordinary SCC of the esophagus. Thus, it might be possible for mucosal BSCs to be indicated for endoscopic therapy.

The rate of BSC located in the cervical esophagus is low and about 60% of lesions are in the middle esophagus[10]. Although EMRC for lesions in the cervical esophagus is generally difficult, we successfully resected the lesion *en bloc* while achieving a sufficient margin. Complete histological evaluation of the *en bloc* specimen is necessary to decide further clinical management. EMRC might be a better method than standard EMR for resection of BSCs because Farrell *et al*[11] reported that EMRC resulted in deeper histological resection than standard EMR.

Some investigators reported that superficial BSCs form small submucosal tumors. This finding might be a feature of the early stage of BSCs because they develop in the basal mucosal layer and invade the LPM and grew expansively. Our lesion was covered with normal squamous cells on the surface and the invasion depth was limited to the MM. BSC would grow upward, whereas BSCs invade deeper layers such as the submucosal or muscular layers.

It is reported that the microvascular pattern detected by ME-NBI is useful to diagnose the depth of tumor invasion of esophageal SCC[5,12]. As the cancer invades deeper into the mucosa, the intrapapillary capillary loops (IPCLs) become more dilated and elongated. When tumors invade the MM, the regular arrangement of IPCLs collapses and an avascular area surrounded by tumor vessels emerges. Arima *et al*[13] reported that these findings by ME-NBI could be employed for BSC as well. In this case, we diagnosed that the depth of tumor invasion was limited to within the MM and the histopathological findings for the resected specimen were identical. BSC limited to the MM in the cervical esophagus can be successfully resected *en bloc* by EMRC. Careful follow-up is necessary, though the rate of lymph node metastasis seems to be very low.

REFERENCES

1 **Wain SL**, Kier R, Vollmer RT, Bossen EH. Basaloid-squamous carcinoma of the tongue, hypopharynx, and larynx: report of 10 cases. *Hum Pathol* 1986; **17**: 1158-1166
2 **Soriano E**, Faure C, Lantuejoul S, Reyt E, Bolla M, Brambilla E, Righini CA. Course and prognosis of basaloid squamous cell carcinoma of the head and neck: a case-control study of 62 patients. *Eur J Cancer* 2008; **44**: 244-250
3 **Akagi I**, Miyashita M, Makino H, Nomura T, Ohkawa K, Tajiri T. Basaloid squamous cell carcinoma of the esophagus: report of two cases. *J Nihon Med Sch* 2008; **75**: 354-360
4 **Tsukayama S**, Hirano M, Murakami N, Uno Y, Nozawa H, Yoshino H, Orta N, Kikkawa H, Masuda S. A case report of basaloid-squamous carcinoma of the esophagus (in Japanese with English abstract). *Nippon Shokaki Geka Gakkai Zasshi* 2000; **33**: 462-466
5 **Arima M**, Tada M, Arima H. Evaluation of microvascular patterns of superficial esophageal cancers by magnifying endoscopy. *Esophagus* 2005; **2**: 191-197
6 **Japanese Society for Esophageal Diseases**. Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus. 9th ed. Tokyo: Kanahara, 2001
7 **Suzuki H**, Nagayo T. Primary tumors of the esophagus other than squamous cell carcinoma--histologic classification and statistics in the surgical and autopsied materials in Japan. *Int Adv Surg Oncol* 1980; **3**: 73-109
8 **Lam KY**, Law S, Luk JM, Wong J. Oesophageal basaloid squamous cell carcinoma: a unique clinicopathological entity with telomerase activity as a prognostic indicator. *J Pathol* 2001; **195**: 435-442
9 **Mori K**, Ishii K. A case of superficial basaloid carcinoma of the esophagus (in Japanese). *Nihon Gekakei Rengo Gakkaishi* 2008; **33**: 742-745
10 **Ishii A**, Chino O, Nishi T. Clinicopathological evaluation of basaloid carcinoma of the esophagus on endoscopic diagnosis (in Japanese with English abstract). *Nippon Shokaki Naishikyou Gakkai Zasshi* 2007; **49**: 2953-2961
11 **Farrell JJ**, Lauwers GY, Brugge WR. Endoscopic mucosal resection using a cap-fitted endoscope improves tissue resection and pathology interpretation: an animal study. *Gastric Cancer* 2006; **9**: 3-8
12 **Kumagai Y**, Toi M, Inoue H. Dynamism of tumour vasculature in the early phase of cancer progression: outcomes from oesophageal cancer research. *Lancet Oncol* 2002; **3**: 604-610
13 **Arima H**, Arima M, Tada T. Microvascular patterns of esophageal micro squamous cell carcinoma on magnifying endoscopy. *Dig Endosc* 2008; **20**: 6-11

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CASE REPORT

Drug associated vanishing bile duct syndrome combined with hemophagocytic lymphohistiocytosis

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Abstract

A 28-year-old woman with untreated autoimmune disorder, demonstrated skin rash and fever after taking Amoxicillin-clavulanate and developed progressive jaundice. A bone marrow aspiration indicated an increased number of macrophages with hemophagocytosis and liver biopsy showed pure centrilobular cholestasis with necrosis and some absence of portal bile ducts. Furthermore, a serological test for Epstein-Barr virus was positive. Under treatment by liver dialysis and administration of steroids led to rapidly defervescence and clinical improvement. However, liver enzymes were still markedly elevated with persistent anemia, even after immunosuppressive treatment. The patient is currently waiting for liver transplantation. This is the first description of vanishing bile duct syndrome combined with hemophagocytic lymphohistiocytosis, with underlying causes including infection, drug-induced factors and untreated autoimmune disorder.

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Key words: Vanishing bile duct syndrome; Hemophagocytic lymphohistiocytosis; Epstein-Barr virus; Amoxicillin-clavulanate

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a group of disorders of the mononuclear phagocyte system that are characterized by histiocyte proliferation and hemophagocytosis, resulting in fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, liver dysfunction, and coagulopathy. Vanishing bile duct syndrome (VBDS) is another severe cholestatic disease characterized by progressive loss of small intrahepatic ducts, caused by a variety of diseases and leading to chronic cholestasis, cirrhosis, and premature death from liver failure. Multiple similar etiologies of these two types of disease have been described including neoplastic, infectious, autoimmune, and medication/toxin mediated routes. However, concurrent diagnoses of HLH and VBDS have not previously been reported. Here, we describe a case of HLH combined with VBDS, with underlying causes including infection, drug-induced factor and untreated autoimmune disorder.

CASE REPORT

A 28-year-old Chinese woman was transferred to our

hospital with persistent fever and progressive jaundice. The presentations were preceded by mild upper respiratory tract infection 2 wk earlier. She took a single dose of Amoxicillin-clavulanate for the upper respiratory tract infection, after which a skin rash developed on her back, arms and thighs and jaundice appeared gradually. After admission to hospital, the patient suddenly developed high fever, marked by remittent fever up to 40.5 ℃, as well as progressive obstructive jaundice. Physical examination showed no signs of infection or hematological disease, and was only notable for hepatosplenomegaly. Laboratory studies showed normal white blood cell levels, but progressive decline of hemoglobin and platelets; elevated liver enzymes (alanine aminotransferase 408 U/L, normal 0-37 U/L; aspartate aminotransferase 608 U/L, normal 0-40 U/L); elevated bilirubin (839 μmol/L, normal 0-22.6 μmol/L); elevated ferritin level (> 40 000 μg/L, normal 16-313 ug/L); hypertriglyceridemia (4.58 mmol/L, normal 0.33-1.77 mmol/L); prolonged prothrombin time and activated partial thromboplastin time; normal complement level; ANA > 1:5120; Anti-dsDNA antibody, ENA, anti-SSA antibody, ribonuclear protein antibody and Epstein-Barr virus (EBV)-IgG were positive. Serology for human immunodeficiency virus, hepatitis A, B, and C, tubercle bacillus, and hemococcidium were negative. Computed tomography (CT) scan and magnetic resonance cholangiopancreatography of the upper abdomen revealed a normal extrahepatic biliary tree. Skin biopsies were non-specific and immunohistochemical staining was negative. Liver biopsy showed pure centrilobular cholestasis with necrosis and some absence of portal bile ducts. Repeat bone marrow aspirations revealed hemophagocytosis by macrophages, without any evidence of hematologic malignancy. Positron emission tomography-CT indicated non-cancerous proliferative. The patient had a 2-year history of ANA 1:1280, without any clinic manifestation and a history of immunodeficiency, and denied allergies to previously used medications including antibiotics.

The patient's combination of clinical features (fever, hepatosplenomegaly) and laboratory evaluation (cytopenia in peripheral blood, hypertriglyceridemia, elevated ferritin, and hemophagocytosis in bone marrow without any obvious evidence of malignancy) fulfilled the diagnosis criteria for HLH. A diagnosis of VBDS, combined with drug-associated HLH was made. She was treated with pulsed methylprednisolone (1000 mg/d for 3 d), intravenous immunoglobulins (0.4 g/kg per day for 3 d), ursodeoxycholic acid and immediate blood transfusion. In addition, although methylprednisolone was followed by oral prednisolone 50 mg/d, the fever and symptoms still persisted. Considering the patient's desire for fertility, further immunosuppressive treatment was not administered immediately. Later, the patient was put on the artificial liver support system treatment and given 3 rounds of immunoadsorption therapy, after which she rapidly defervesced and improved clinically. However, bilirubin levels were elevated soon after liver dialysis and the patient therefore agreed to immunosuppressive therapy. In addition to methylprednisolone, the combination therapy of cyclophosphamide (400 mg once weekly) and mycophenolate mofetil (1.5 g/d) were continued for approximately 6 wk, with the addition of closporine A. This was eventually suspended because of repeated gastrointestinal bleeding. Thereafter, 6 mo after presentation, liver enzymes were still markedly elevated with persistent anemia. The patient is currently waiting for liver transplantation.

DISCUSSION

HLH is a life threatening clinic and pathologic disorder, in which impaired or ineffective T cells and natural killer lymphocyte cells are activated. This results in hypercytokinemia leading to uncontrolled activation of benign scavenger macrophages and development of hemophagocytosis in the reticuloendothelial system[1]. In most cases, HLH is not a single disease but is frequently associated with infections, malignancies or rheumatological disorders[2]. HLH has been associated with various infections, of which EBV appears to be the most commonly associated triggering infection[3-5]. Associated rheumatic disorders have included rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, mixed connective tissue disease[4-6]. Drug induced hypersensitivity reaction may include hemophagocytic syndromes, with or without reactivation of EBV[7-9]. Regardless of the etiology, the cardinal clinical signs are prolonged fever, which is unresponsive to antibiotics, and hepatosplenomegaly. A third of the patients' neurological signs, such as irritability, altered consciousness, seizures, and signs of increased intracranial pressure, can be present[10,11]. On histological examination, erythrophagocytosis in HLH is commonly present in lymphoid tissues (liver, spleen, and bone marrow), but rarely evident in skin biopsy specimens. However, phagocytic activity in liver, spleen and marrow biopsy specimens is not universally present. Only one third of initial bone marrow biopsy specimens demonstrate hemophagocytosis[12].

In 1991, the International Histiocyte Society established diagnostic guidelines in an effort to facilitate early diagnosis and management[13]. According to the updated guideline, the diagnosis of HLH is definitive[14,15]. On the other hand, in contrast to the complex origins of HLH, drug-induced cholestasis has its definite inducing agent. Cholestasis can occur with nearly all classes of drugs although antibiotics seem to be responsible more often than other groups. The most often reported culprits are erythromycin and amoxycillin-clavulanate[16]. The most severe form of cholestatic injury is VBDS. This condition is characterized by progressive ductopenia with portal tract fibrosis that leads to secondary liver cirrhosis with a complete absence of small bile ducts. Drug induced ductopenia has been described to continue long after the offending drug is withdrawn[17]. The syndrome is extremely rare, representing 0.5% of small bile duct disease[18].

Results of the international consensus protocol sponsored by the Histiocyte Society for treatment of patients newly diagnosed with HLH (HLH-94) were published in 2005. The goals of the trial were to achieve clinical remission of the life-threatening inflammation and to provide potentially curative therapy through allogenic hematopoe-

itic cell transplantation. HLH can be rapidly fatal in the absence of specific intervention bleeding; infection and progressive cerebral damage are the usual causes of death. Therefore, it is recommended that treatment should be started when there is a high degree of clinical suspicion, even when results of diagnostic studies are still pending[19]. Today, effective initial therapy of HLH consists of combinations of proapoptotic chemotherapy and immunosuppressive drugs targeting the hyperactivated T cells and histiocytes[20]. The recommended treatment consists of a combination of etoposide and dexamethasone (for central nervous system penetration), with or without intrathecal methotrexate, followed by maintenance therapy with the addition of closporine A. Projected survival rates, 5 years from diagnosis, range from 50% to 70%[21].

By comparison, therapy of toxin or drug-induced bile duct injury has remained largely ineffective and is mainly limited to the treatment of symptoms and the consequences of prolonged cholestasis. Corticosteroids have been invariably ineffective. The role of ursodeoxycholic acid remains controversial[22]. Although ursodeoxycholic acid has also been shown to be effective in other cases of VBDS related to drugs, it remains ineffective in cases of bile duct damage related to amoxicillin-clavulanate, as in the current case[23,24]. Liver transplantation is obviously the only alternative in patients who develop secondary biliary cirrhosis and liver failure.

In conclusion, immune-mediated destruction triggered by drugs is the underlying mechanism common to both HLH and VBDS, and antibiotics have been linked to both of these conditions. The initial episode seems to be the result of a direct hypersensitivity disorder. This is the first description of a diagnosis of VBDS combined with HLH. This case illustrates the importance of considering all possible underlying causes in a patient, including an infectious etiology, a drug-induced factor and an underlying immunologically mediated reaction. The co-existence of VBDS and HLH suggests that common pathogenic mechanisms are involved, with excessive activation of T lymphocytes or cytokine storm[24,25].

REFERENCES

1 **Filipovich AH**. Hemophagocytic lymphohistiocytosis and related disorders. *Curr Opin Allergy Clin Immunol* 2006; **6**: 410-415
2 **Chang CS**, Wang CH, Su IJ, Chen YC, Shen MC. Hematophagic histiocytosis: a clinicopathologic analysis of 23 cases with special reference to the association with peripheral T-cell lymphoma. *J Formos Med Assoc* 1994; **93**: 421-428
3 **Rouphael NG**, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; **7**: 814-822
4 **Filipovich AH**. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. *Immunol Allergy Clin North Am* 2008; **28**: 293-313, viii
5 **Tristano AG**. Macrophage activation syndrome: a frequent but under-diagnosed complication associated with rheumatic diseases. *Med Sci Monit* 2008; **14**: RA27-RA36
6 **Lambotte O**, Khellaf M, Harmouche H, Bader-Meunier B, Manceron V, Goujard C, Amoura Z, Godeau B, Piette JC, Delfraissy JF. Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. *Medicine* (Baltimore) 2006; **85**: 169-182
7 **Ben m'rad M**, Leclerc-Mercier S, Blanche P, Franck N, Rozenberg F, Fulla Y, Guesmi M, Rollot F, Dehoux M, Guillevin L, Moachon L. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. *Medicine* (Baltimore) 2009; **88**: 131-140
8 **Komatsuda A**, Okamoto Y, Hatakeyama T, Wakui H, Sawada K. Sulfasalazine-induced hypersensitivity syndrome and hemophagocytic syndrome associated with reactivation of Epstein-Barr virus. *Clin Rheumatol* 2008; **27**: 395-397
9 **Gutiérrez-Ravé Pecero VM**, Luque Márquez R, Ayerza Lercundi MA, Fernández Jurado A. Phenytoin-induced hemocytophagic histiocytosis indistinguishable from malignant histiocytosis. *South Med J* 1991; **84**: 649-650
10 **Goo HW**, Weon YC. A spectrum of neuroradiological findings in children with haemophagocytic lymphohistiocytosis. *Pediatr Radiol* 2007; **37**: 1110-1117
11 **Takahashi S**, Oki J, Miyamoto A, Koyano S, Ito K, Azuma H, Okuno A. Encephalopathy associated with haemophagocytic lymphohistiocytosis following rotavirus infection. *Eur J Pediatr* 1999; **158**: 133-137
12 **Favara BE**. Hemophagocytic lymphohistiocytosis: a hemophagocytic syndrome. *Semin Diagn Pathol* 1992; **9**: 63-74
13 **Henter JI**, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. *Semin Oncol* 1991; **18**: 29-33
14 **Henter JI**, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**: 124-131
15 **Janka GE**. Hemophagocytic syndromes. *Blood Rev* 2007; **21**: 245-253
16 **Juricic D**, Hrstic I, Radic D, Skegro M, Coric M, Vucelic B, Francetic I. Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. *Basic Clin Pharmacol Toxicol* 2010; **106**: 62-65
17 **Degott C**, Feldmann G, Larrey D, Durand-Schneider AM, Grange D, Machayekhi JP, Moreau A, Potet F, Benhamou JP. Drug-induced prolonged cholestasis in adults: a histological semiquantitative study demonstrating progressive ductopenia. *Hepatology* 1992; **15**: 244-251
18 **Ludwig J**. Idiopathic adulthood ductopenia: an update. *Mayo Clin Proc* 1998; **73**: 285-291
19 **Morrell DS**, Pepping MA, Scott JP, Esterly NB, Drolet BA. Cutaneous manifestations of hemophagocytic lymphohistiocytosis. *Arch Dermatol* 2002; **138**: 1208-1212
20 **Henter JI**, Samuelsson-Horne A, Aricò M, Egeler RM, Elinder G, Filipovich AH, Gadner H, Imashuku S, Komp D, Ladisch S, Webb D, Janka G. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002; **100**: 2367-2373
21 **Horne A**, Janka G, Maarten Egeler R, Gadner H, Imashuku S, Ladisch S, Locatelli F, Montgomery SM, Webb D, Winiarski J, Filipovich AH, Henter JI. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. *Br J Haematol* 2005; **129**: 622-630
22 **Duerksen DR**, Van Aerde JE, Gramlich L, Meddings JB, Chan G, Thomson AB, Clandinin MT. Intravenous ursodeoxycholic acid reduces cholestasis in parenterally fed newborn piglets. *Gastroenterology* 1996; **111**: 1111-1117
23 **O'Brien CB**, Shields DS, Saul SH, Reddy KR. Drug-induced vanishing bile duct syndrome: response to ursodiol. *Am J Gastroenterol* 1996; **91**: 1456-1457
24 **Moradpour D**, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, Schmid M. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. *Hepatology* 1994; **20**: 1437-1441
25 **Lambotte O**, Costedoat-Chalumeau N, Amoura Z, Piette JC, Cacoub P. Drug-induced hemophagocytosis. *Am J Med* 2002; **112**: 592-593

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Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

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Las Vegas, NV 89085, United States

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December 1-4, 2012
Advances in Inflammatory Bowel Diseases
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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

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Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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