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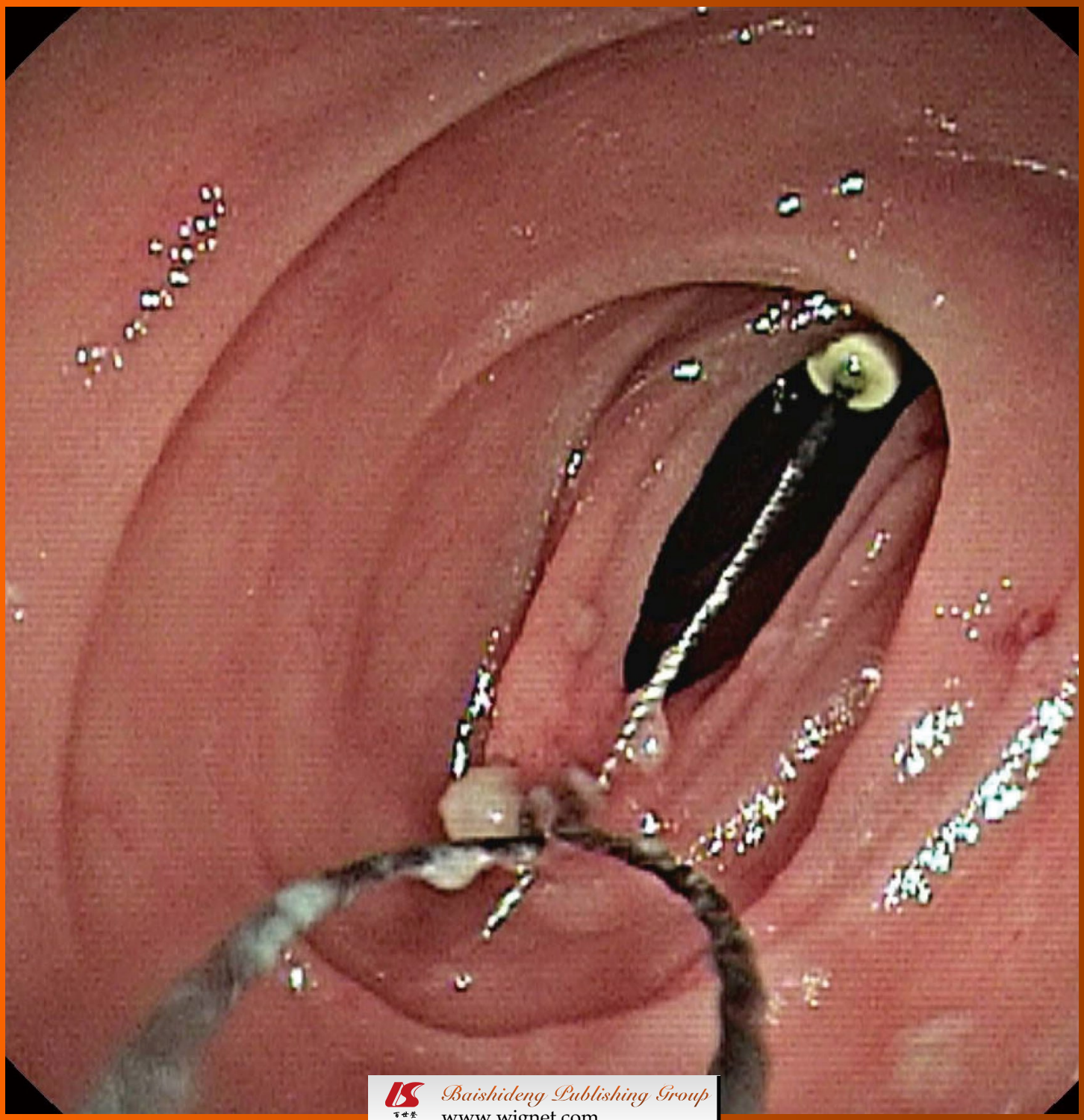

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EDITORIAL

Management of complications following endoscopic submucosal dissection for gastric cancer

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Abstract

Endoscopic treatment should be considered for early gastric cancer (EGC) and gastric precancerous lesions. Endoscopic submucosal dissection (ESD) was developed for en bloc removal of a large gastric neoplasm and has been developed following improvements in electrical equipment for hemostasis and dissection and with advances in various knives, hemostatic forceps and endoscopic equipment. ESD is currently the treatment of choice for precancerous lesions or EGC showing mucosal invasion. Hemorrhage and perforation are major complications of ESD for EGC. We describe the complication of ESD procedures in gastric lesions for endoscopists who are relatively inexperienced in ESD and who may lack optimal access to ESD education and facilities.

Key words: Endoscopic submucosal dissection; Gastric cancer, Perforation; Bleeding

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INTRODUCTION

The incidence of gastric cancer is high in Japan, Korea and China. Periodic endoscopy should be performed. Endoscopic treatment should be considered for early gastric cancer (EGC) and gastric precancerous lesions. Endoscopic submucosal dissection (ESD) has been developed following improvements in electrical equipment for hemostasis and dissection and with advances in various knives, hemostatic forceps and endoscopic equipment. ESD is currently the treatment of choice for precancerous lesions or EGC showing mucosal invasion[1,2].

Professional endoscopic skill, experience with the electronic equipment, knowledge of the appropriate application of diverse knives and skillful endoscopy assistants are required to achieve positive outcomes with ESD. Even when these conditions are met, complications such as hemorrhage, perforation, pneumothorax, aspiration pneumonia, cardiopulmonary complication, abdominal pain and fever can occur. The endoscopist must possess sufficient knowledge to address such complications promptly and appropriately. A thorough knowledge of the indicators for ESD and the factors causing these complications is also important. Hemorrhage is a complication in 10%-20% of ESDs[3] and perforation in 5%[4]; most of these cases can be overcome, however, through skilled execution of the endoscopic procedure[5]. The en bloc resection rate for EGC is nearly 80%, depending on the location and size of the lesion; such resection prevents recurrence of the cancer in nearly all cases[6,7]. These data were collected at large-scale hospitals for the preparation of ESD educational curricula and primarily include pro-

cedures performed with ample access to the most advanced equipment, skillful endoscopy care teams and gastrointestinal specialists.

A rapidly increasing number of physicians are entering the field of endoscopy and many hospitals are opening new endoscopy facilities. However, most have inadequate educational systems and endoscopic equipment. Although many academic meetings and workshops have sought to address these problems, the tremendous and rapidly increasing demands are difficult to meet. In this context, we present our opinions and suggestions for the management of hemorrhage and perforation complications of ESD in this article. We hope that this discussion may benefit endoscopists who are relatively inexperienced in ESD for stomach lesions and who may lack optimal access to ESD education and facilities.

HEMORRHAGE

During ESD, the endoscopist must identify the blood vessels most likely to hemorrhage and treat them effectively to stop the hemorrhage while dissecting the submucosa. ESD must not be attempted on a lesion affecting vessels in which an endoscopist cannot consistently stop bleeding in gastrointestinal hemorrhage patients. Hemostasis is usually most difficult in the upper stomach due to the broad distribution of large blood vessels and re-bleeding occurs readily in this location when the gastrointestinal tract bleeds. Oda *et al* reported that only location (upper and middle third) and size (≥ 31 mm) were associated with immediate bleeding[8]. In one report, younger age and the location of the lesions (upper and middle third) were associated with a higher frequency of immediate bleeding[9]. Bleeding can be somewhat reduced in areas with abundant blood vessels by strengthening the coagulation energy when precutting or dissection, but this increases the risk of perforation. Thus, the degree of mucosal elevation following submucosal dissection should be assessed carefully. During ESD, the endoscopist should not waste time attempting to achieve hemostasis or control minor bleeding, and should not interfere with complete incision by applying a clip. Dissection of lesions itself has an effect of hemostasis and is a help for obtaining sight.

In 4%-6% of cases, delayed bleeding occurs 24 h or more after ESD and can have serious consequences[10]. Delayed bleeding frequently follows ESD performed on large and flat lesions in the upper stomach[11]. Even in cases where no bleeding is observed after complete resection, additional coagulation can reduce the risk of delayed bleeding[12]. However, this process can occasionally cause delayed perforation[13]. When almost no submucosal layer remains and the muscle is properly exposed, it is not necessary to practice preventive hemostasis. Bleeding following the resection of lesion should be addressed using light lifting with hemostatic forceps to reduce muscle damage. The attempt to achieve hemostasis in coagulation mode by pressing the lesion, such as in ulcers, is associated with a very high risk of perforation. For patients at risk of delayed bleeding, insertion of an L-tube after the procedure will allow any such bleeding to be discovered and addressed immediately.

Most bleeding after ESD can be treated with an endoscopic procedure using an electronic knife, a hemoclip, argon plasma coagulation and hemostatic forceps. If the hemostasis is delayed due to difficult lesion or incomplete field of view, cardiopulmonary instability might occur in the patient. In this situation, it is important not to hesitate to carry out emergency surgery or embolization.

Patients with chronic renal failure or liver cirrhosis and recipients of subtotal gastrectomies are at high risk of acute and/or delayed bleeding. Because a patient's condition can deteriorate suddenly during bleeding, novice endoscopists should not attempt endoscopic procedures to treat hemorrhage. Patients who take anticoagulants or antiplatelet agents for lower risk cardiovascular or cerebrovascular disease should stop these medications 1 wk before an endoscopic procedure to reduce the risk of bleeding[14].

PERFORATION

In one report, location in the middle portion of the stomach ($P = 0.028$) and an elevated lesion ($P = 0.0477$) were significantly associated with the development of a perforation[15]. Appropriate use of high-frequency electronic equipment and instruments and the administration of sufficient submucosal injections are necessary to prevent perforation. The degree of submucosal injection should be evaluated during dissection; if mucosal elevation is insufficient, additional injection is necessary. If a patient complains of pain during ESD or hemostatic procedures, muscle involvement is possible and the direction of incision or degree of visibility may require correction. The use of sodium hyaluronate allows the elevation of the lesion to be maintained for a longer period of time, aiding dissection[16].

If perforation occurs and demands the attention of the endoscopist before lesion dissection, complete resection will be impossible and a subsequent surgical procedure will be required. A strategic approach is thus necessary. Most perforation can be addressed with a hemoclip but this instrument may make it difficult to obtain a sufficient resection margin or perform en bloc resection. Thus, it is desirable to apply clips to perforated areas after an incision or exfoliation has been performed and sufficient space for complete resection has been created. If the perforated area is large or the incision or exfoliation takes too long, pneumoperitonium can cause serious secondary problems such as respiratory failure, decreased blood pressure or increased abdominal pain. Centesis should thus be performed with an 18-20 gauge puncture needle to remove air from the abdominal cavity and to provide sufficient time for a complete resection attempt[17].

Although clipping is the most common treatment for perforation, a hemoclip can obscure visibility of structur-

es such as the gastroesophageal junction and the posterior wall of the upper gastric body. Band ligation may thus be a preferable treatment option[18]. Additionally, a clip may not encompass a wide perforation; in such cases, suction of the omentum can be applied to aid the clipping of the perforated area. When the omentum is not sucked after clipping of the perforation margins, clips on opposite sides of the perforation may be tied together with a detachable snare to treat a large perforation.

Following endoscopic treatment of a perforation, the patient may have leukocytosis, tenderness and/or a slight fever for 1-2 d. Most perforations that occur during ESD can be treated conservatively with the administration of antibiotics; few cases require surgical operation[19]. Because the conditions of the elderly, immunocompromised or chronic-disease patients may be exacerbated by perforation, careful observation of these patients is necessary and abdominal computed tomography (CT) scans should be performed if peritonitis is suspected. A surgical operation should be performed in cases of peritonitis.

Although pneumothorax is a rare complication, it can lead to death if appropriate measures are not taken promptly. Perforation of esophageal, gastroesophageal junction or fundus lesions can occur with respiration or sudden movement during precutting and may cause pneumoperitonium and pneumothorax simultaneously[20]. Because sudden respiratory failure may occur in such cases, all procedures should be stopped and the insertion of a chest tube into the pleural space should be considered. A novice endoscopist should consider the difficulty of each procedure and the risks of bleeding and perforation and transfer difficult or risky cases to a specialist endoscopy center. This is particularly true for lesions of the gastroesophageal junction, cardia and fundus. Expert endoscopists should also consider operating on such lesions under general anesthesia to control the movement and breathing of the patient, especially when the lesions are large.

ESD is an attractive and effective treatment for gastric cancer. Complications such as bleeding, perforation and incomplete resection may occur but can be minimized with the development of the endoscopist's skill and the use of advanced equipment. Realistically, however, opportunities to learn and practice ESD and use optimal equipment are often limited. We recommend the implementation of an appropriate educational system. The ability of the endoscopist to perform a procedure, the condition of available equipment and instrumentation, the position and size of the lesion, the health of the patient and the limitations of ESD should all be considered when evaluating the use of this procedure.

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Assessment of gastroesophageal reflux disease by serodiagnosis of *Helicobacter pylori*-related chronic gastritis stage

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Abstract

AIM: To evaluate the association of *Helicobacter pylori* (*H.pylori*)-related chronic gastritis stage with upper gastrointestinal symptoms and gastroesophageal reflux disease (GERD).

METHODS: Subjects underwent upper gastrointestinal endoscopy, a questionnaire using a frequency scale for symptoms of GERD (FSSG), and measurements of serum *H.pylori*-antibody and pepsinogen (PG) levels. They were classified into the following 4 groups in terms of *H.pylori*-related chronic gastritis stage: Group A (n = 219), *H.pylori*(-)PG(-); Group B (n = 310), *H.pylori*(+)PG(-); Group C (n = 279), *H.pylori*(+)PG(+); and Group D (n = 17), *H.pylori*(-)PG(+).

RESULTS: Reflux esophagitis occurred in 30.6% of Group A, 14.5% of Group B, 6.8% of Group C, and 0% of Group D ($P < 0.001$). Scores for acid reflux symptoms decreased significantly with chronic gastritis stage (from Group A to D) ($P < 0.05$), while scores for dysmotility symptoms did not differ significantly. The prevalence of non-erosive reflux disease (NERD) did not differ among groups. However, in subjects with GERD, the prevalence of NERD tended to increase with chronic gastritis stage ($P = 0.081$).

CONCLUSION: Acid reflux symptoms and the prevalence of reflux esophagitis can be assessed by measuring both serum *H.pylori*-antibody and PG levels.

Key words: Gastroesophageal reflux disease; *Helicobacter pylori*; Pepsinogen; Screening and diagnosis

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INTRODUCTION

Gastroesophageal reflux disease (GERD) includes not only reflux esophagitis (RE) confirmed by upper gastrointestinal endoscopy, but also non-erosive reflux disease (NERD) characterized only by subjective symptoms, such as heartburn without RE. The Montreal definition was presented as the worldwide consensus on GERD in 2006[1] and is based mostly on subjective symptoms: "GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications". According to this definition, GERD is further classified into esophageal syndrome and extraesophageal syndrome, and a wide variety of symptoms are present. Thus, closer examination of subjective symptoms is required in differentiating GERD from other organic digestive tract diseases.

Questionnaires are effective in ascertaining the subjective symptoms of GERD patients. Many GERD-specific questionnaires have been developed[2], including the questionnaire for the diagnosis of reflux diseases[3], which is the most widely used of these questionnaires around the world. In Japan, Kusano *et al* developed the frequency scale for symptoms of GERD (FSSG)[4], a scale that has been used for early diagnosis and therapy assessment. Of the 12 FSSG questions, 7 questions deal with acid reflux symptoms, and the remaining 5 questions deal with gastrointestinal dysmotility symptoms, allowing GERD to be assessed by symptom group[5]. Assessing upper gastrointestinal symptoms by broadly dividing them into two groups is not only useful for planning treatment strategy for GERD[6], but it is also important for objectively analyzing the disease state.

By measuring two serum parameters, the *Helicobacter pylori* (*H.pylori*) antibody (Ab) titer and the serum pepsinogen (PG) level as a screening test for extensive chronic atrophic gastritis (CAG)[7], we have graded *H.pylori*-related chronic gastritis into four stages from A to D: Group A, *H.pylori*-negative/PG-negative; Group B, *H.pylori*-positive/PG-negative; Group C, *H.pylori*-positive/PG-positive; and Group D, *H.pylori*-negative/PG-positive. Group A included *H.pylori* non-infected healthy subjects. Group B showed established *H.pylori* infection, but without CAG. Group C had CAG. Group D had severe intestinal metaplasia due to progression of CAG, but *H.pylori* had been spontaneously eliminated, representing so-called metaplastic gastritis. CAG advances from A to B to C, and then to D. We have documented that the incidence of gastric cancer gradually increases with chronic gastritis progression[8,9,10]. This has enabled screening of high-risk patients for gastric cancer based on serodiagnosis. An inverse relationship has been reported between CAG and RE onset[11], and many studies have found that the incidence of *H.pylori* infection is lower in Japanese RE patients than in healthy individuals (control group)[12-14]. A study found that NERD is closely related to *H.pylori* infection and progression in gastric mucosal atrophy[15]. Moreover, one study found a negative correlation between GERD and the anti-*H.pylori*-Ab positive rate[16], while another study documented that *H.pylori* infection was unrelated to GERD and was neither an exacerbating factor nor a preventive factor[17]. To the best of our knowledge, no studies have used GERD-specific questionnaires to quantify acid reflux and gastrointestinal dysmotility symptoms and to closely examine the relationships between *H.pylori*-related chronic gastritis progression and upper gastrointestinal symptoms.

In routine clinical care, performing endoscopy on all patients complaining of upper gastrointestinal symptoms is difficult, and some supplementary parameters would be useful to gather more information to make the diagnosis of GERD. The aim of this study was to examine the relationship of *H.pylori* and PG status with GERD.

MATERIALS AND METHODS

Study subjects

In Japan, health checkup programs are performed to identify selected diseases (e.g., gastric cancer) in their early stages of development. Both symptom-free subjects and subjects showing specific symptoms took part in upper gastrointestinal endoscopic examinations at our institution. Between January 2006 and March 2008, a total of 1165 factory workers (1147 males, 18 females) ranging in age from 40 to 70 years who underwent upper gastrointestinal endoscopy and completed the FSSG questionnaire were enrolled. In addition, all enrolled subjects underwent serological testing and their *H.pylori*-Ab titers and serum PG levels were measured. Subjects who had a previous history of surgical resection of the stomach, *H.pylori* eradication, or those who had been prescribed a proton pump inhibitor (PPI), which might affect gastrointestinal function, were excluded from the study. Furthermore, subjects with and without *H.pylori* infection were selected for the study using serum-specific antibody titers as described in the following section. Thus, 825 subjects (812 males, 13 females) were eligible for this study. The ethics committee of Wakayama Medical University approved the study protocols.

Diagnosis of H.pylori infection and extensive CAG by serological tests

H.pylori-Ab titers were measured using an enzyme-linked immunosorbent assay (ELISA) (MBL, Nagoya, Japan)[18]. In the present study, *H.pylori*-Ab titers $\geq$ 50 U/mL were taken to be *H.pylori*-positive, and $<$ 30 U/mL indicated *H.pylori*-negative. *H.pylori*-Ab titers $\geq$ 30 but $<$ 50 U/mL were considered unclassifiable, and subjects showing titers within this range were excluded from *H.pylori* infection

Table 1 Relationship between *H.pylori* infection or serum PG test and upper abdominal symb to ms erosive reflux esophagitis

	H.pylori infection		*P* value	Serum PG		*P* value
	-	+		-	+	
n	236	589		529	296	
FSSG						
-total score (mean ± SD)	3.58 ± 4.00	3.17 ± 3.90	0.175	3.45 ± 3.96	2.99 ± 3.87	0.104
-acid reflux score (mean ± SD)	1.78 ± 2.21	1.62 ± 2.32	0.350	1.79 ± 2.33	1.45 ± 2.20	0.038
-dysmotility score (mean ± SD)	1.80 ± 2.32	1.55 ± 1.99	0.127	1.66 ± 2.14	1.54 ± 2.02	0.432
Erosive esophagitis (LA grade A-D)	28.4%(67/236)	10.7%(63/589)	0.000	21.2%(112/529)	6.1%(18/296)	0.000
FSSG total score ≥ 8 (= GERD)	13.6%(32/236)	11.7%(69/589)	0.465	13.8%(73/529)	9.5%(28/296)	0.076
FSSG total score ≥ 8 and non-erosive esophagitis (= NERD)	8.1%(19/236)	9.5%(56/589)	0.510	9.8%(52/529)	7.8%(23/296)	0.377
NERD/GERD	59.4%(19/32)	81.2%(56/59)	0.027	71.2%(52/73)	82.1%(23/28)	0.317

H.pylori: *Helicobacter pylori*; PG: pepsinogen; CAG: chronic atrophic gastritis; FSSG: frequency scale for symptoms of gastroesophageal reflux disease; SD: standard deviation; LA: Los Angeles classification; GERD: gastroesophageal reflux disease; NERD: non-erosive reflux disease.

assessment. The sensitivity and specificity of the ELISA test used in this study were 93.5% and 92.5%, respectively[18]. Serum PG levels were measured by radioimmunoassay (Dainabot, Tokyo, Japan)[19]. PG, a measure of gastric atrophy, was considered positive for values of PG Ⅰ ≤ 70 μg/L with a PG Ⅰ/Ⅱ ratio of ≤ 3[20,21]. These criteria offer a sensitivity of 70.5% and a specificity of 97% for the diagnosis of extensive CAG, using pathological diagnosis as the gold standard[20]. Subjects for whom both *H.pylori* infection and PG level could be determined were divided into the following four groups in terms of *H.pylori*-related chronic gastritis stage: Group A, *H.pylori*-negative/PG-negative; Group B, *H.pylori*-positive/PG-negative; Group C, *H.pylori*-positive/PG-positive; and Group D, *H.pylori*-negative/PG-positive[8].

Endoscopic findings of RE

RE was diagnosed by upper gastrointestinal endoscopy. According to the Los Angeles classification system[22], Grades A through D indicate erosive esophagitis. In the present study, only patients with erosive esophagitis were diagnosed with RE, and subjects with Grade M (minimal change)[23]or Grade N were not diagnosed with RE. Hiatal hernia was diagnosed endoscopically when the distance between the crural impression and the gastroesophageal junction was 2 cm or more.

Assessment of FSSG questionnaire and determination of GERD

Using the FSSG questionnaire, subjective symptoms of GERD were quantified, and total, acid reflux, and gastrointestinal dysmotility scores were calculated. GERD was defined as a total score ≥ 8, which is the recommended cut-off FSSG value for GERD[4]. Furthermore, NERD was defined as total score ≥ 8 without endoscopic erosive esophagitis.

Statistical analysis

All data analyses were performed using SPSS version 11.0 software (SPSS, Chicago, IL, USA). Pair-wise differences in the FSSG score were analyzed using the unpaired Student's *t*-test, and overall differences in age and FSSG score were analyzed using the Kruskal-Wallis test. Pair-wise and overall differences in categorical variables were analyzed by Fisher's exact test. All tests were 2-sided, and values of $P < 0.05$ were considered significant. Data are expressed as means ± standard deviation.

RESULTS

Clinical characteristics of study subjects

As mentioned above, of the 1165 subjects in whom *H.pylori*-Ab titers and serum PG levels were measured, those meeting the exclusion criteria were removed. Most of the remaining 825 subjects were men (98.4%) and drinkers (74.9%). Reflecting the high incidence of *H.pylori* infection among middle-aged and elderly individuals in Japan, the incidence of *H.pylori* infection was high (71.4%). With regard to RE, Grade D (the most severe LA grade) was not seen in any subjects, and Grades A and B (mild grades) accounted for 94.6% of cases.

Comparison of upper gastrointestinal symptoms and RE between H.pylori-positive and H.pylori-negative subjects and between PG-positive and PG-negative subjects

The analysis was conducted between *H.pylori*-positive (n = 589) and *H.pylori*-negative (n = 236) subjects and between PG-positive (n = 296) and PG-negative (n = 529) subjects (Table 1). The prevalence of RE was significantly higher for PG- and *H.pylori*-negative subjects than for their positive counterparts ($P < 0.001$). The acid reflux score was significantly higher for PG-negative subjects than for PG-positive subjects ($P < 0.05$), but no significant difference existed between *H.pylori*-positive and -negative subjects. No significant differences in gastrointestinal dysmotility scores between *H.pylori*-positive and -negative subjects or between PG-positive and -negative subjects were present. The prevalence of GERD patients with total FSSG scores ≥ 8 tended to be high for PG-negative subjects ($P = 0.076$), but no significant difference existed between *H.pylori*-positive and -negative subjects. While no significant difference in the prevalence of NERD patients was evident between *H.pylori*-positive and -negative subjects or between PG-positive and -negative subjects, the prevalence of NERD among GERD patients was significantly higher for *H.pylori*-positive subjects ($P = 0.027$).

Table 2 Relationship between the stage of *H.pylori*-related chronic gasrtritis ang upper abdominal symptoms or erosive reflux esophagitis

Stages of *H.pylori*-related chronic gastritis	Group A	Group B	Group C	Group D	Overall
H.pylori infection	-	+	+	-	*P* value
Serum PG test (extensive CAG)	-	-	+	+	
n	219	310	279	17	
Age (years: mean ± SD)	55.23 ± 4.23	55.84 ± 4.08	56.79 ± 3.91	53.94 ± 5.01	0.001
Sex (male/female)	214/5	308/2	273/6	17/0	0.306
Smokers	44.29%	35.16%	41.58%	41.18%	0.164
Drinkers	75.34%	75.48%	74.19%	70.59%	0.939
Serum PG Ⅰ (ng/mL mean ± SD)	59.82 ± 26.52	81.76 ± 48.16	36.59 ± 18.42	21.98 ± 15.99	-
Serum PG Ⅱ (ng/mL mean ± SD)	10.80 ± 5.81	25.89 ± 18.42	20.70 ± 8.60	12.89 ± 4.84	-
PG Ⅰ / Ⅱ	5.70 ± 1.13	3.74 ± 1.31	1.76 ± 0.69	1.53 ± 0.95	-
H.pylori Ig G Aptiter (U/mL mean ± SD)	13.54 ± 5.26	475.31 ± 632.73	441.07 ± 50.94	16.71 ± 6.44	-
FSSG					
-total score (mean ± SD)	3.69 ± 4.01	3.33 ± 3.87	3.00 ± 3.94	2.88 ± 2.55	0.183
-acid reflux score (mean ± SD)	1.83 ± 2.26	1.77 ± 2.39	1.46 ± 2.25	1.29 ± 1.26	0.038
-dysmotility score (mean ± SD)	1.81 ± 2.37	1.56 ± 1.96	1.54 ± 2.03	1.59 ± 1.77	0.800
Erosive esophagitis (LA grade A-D)	30.6%(67/219)	14.5%(45/310)	6.5%(18/279)	0%(0/17)	0.000
LA grade A/B/C/D	45/18/4/0	30/13/2/0	11/6/1/0	0/0/0/0	-
Hiatal hernia	3.2%(7/219)	5.8%(18/310)	7.2%(20/279)	5.9%(1/17)	0.231
FSSG total score ≥ 8 (=GERD)	14.6%(32/219)	13.2%(41/310)	9.7%(28/279)	0%(0/17)	0.177
FSSG total score ≥ 8 and non-erosive esophagitis (=NERD)	8.7%(19/219)	10.6%(33/310)	8.2%(23/279)	0%(0/17)	0.496
NERD/GERD	59.4%(19/32)	80.5%(33/41)	82.1%(23/28)	-	0.081

H.pylori: *Helicobacter pylori*; PG: pepsinogen; CAG: chronic atrophic gastritis; FSSG: frequency scale for symptoms of gastroesophageal reflux disease; SD: standard deviation; LA: Los Angeles classification; GERD: gastroesophageal reflux disease; NERD: non-erosive reflux disease.

Relationship of the stage of H.pylori-related chronic gastritis to upper gastrointestinal symptoms and RE

The stage of *H.pylori*-related chronic gastritis was assessed in the 825 subjects (Table 2). With regard to background factors, significant differences were seen in age. The prevalence of RE showed significant decreases with the stage of the chronic gastritis (from Group A to D) ($P < 0.001$). Acid reflux scores showed a significant decrease with the chronic gastritis stage ($P < 0.05$). The gastrointestinal dysmotility score showed no significant differences between stages ($P = 0.800$). The ratios of GERD patients with total FSSG scores ⩾ 8 showed no significant differences related to the chronic gastritis stage. No significant differences existed in the prevalence of NERD patients among Groups A, B, and C. However, the prevalence of NERD among GERD patients for Groups A, B, and C tended to increase with the chronic gastritis stage ($P = 0.081$).

DISCUSSION

Previously, we have investigated the risk of gastric cancer based on *H.pylori*-related chronic gastritis stage as assessed by a combination of *H.pylori*-Ab titer and serum PG level[8]. The present results suggest that the disease states of GERD and NERD can also be assessed by evaluating the risk for RE and upper gastrointestinal symptoms accompanying gastric acid reflux and gastrointestinal dysmotility. As reported previously[11], the prevalence of RE was low for subjects with CAG. The FSSG was used to closely examine upper gastrointestinal symptoms, and acid reflux scores were low for the group in the advanced stages of *H.pylori*-related chronic gastritis, but no marked difference in gastrointestinal dysmotility scores was seen in relation to the chronic gastritis stage. The prevalence of NERD patients among GERD patients was lowest for Group A and highest for Group C, clarifying the relationship between NERD and the stage of *H.pylori*-related chronic astritis.

Compared to Western countries, the number of GERD patients is lower in Japan, and the prevalence of NERD among GERD patients is higher[24]. Differences exist in the extent of CAG and in its associated reduction in gastric acid secretion that strongly correlate to *H.pylori* infection differences between Japan and Western countries[25], and the present study also showed that they most closely reflected the disease state of GERD in Japan. The prevalence of CagA+ *H.pylori*[26], which correlates pathologically to atrophic gastritis, is particularly high in Japan[27]. This is believed to contribute to differences in the relationship between GERD and *H.pylori* infection[28] in Japan and Western countries[29].

The present study also assessed the difference between *H.pylori*-positive and *H.pylori*-negative subjects and between PG-positive and PG-negative subjects. No significant differences existed in acid reflux and dysmotility scores between *H.pylori*-positive and *H.pylori*-negative subjects. Upper gastrointestinal symptom scores, particularly acid reflux scores, were significantly higher for PG-positive subjects than for PG-negative subjects. No significant differences existed in the prevalence of GERD patients with total FSSG scores ⩾ 8 between *H.pylori*-positive and *H.pylori*-negative subjects, but the prevalence was greater for PG-negative subjects than for PG-positive subjects. GERD-related upper gastrointestinal symptoms are thus more closely influenced by extensive CAG than *H.pylori* infection. However, the finding that the incidence of endoscopy-diagnosed RE for *H.pylori*-negative subjects and PG-negative subjects was higher compared to their

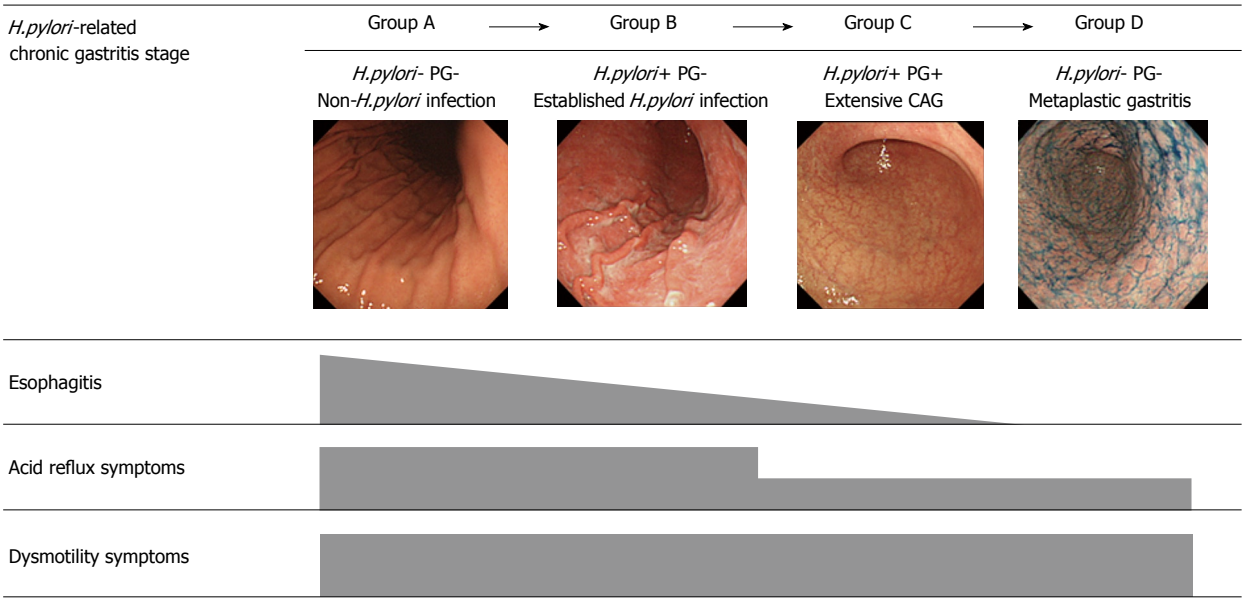

Figure 1 Schematic of the results of this study. *H.pylori: Helicobacter pylori* infection; PG: serum pepsinogen test; CAG: chronic atrophic gastritis.

positive counterparts was very interesting. In other words, reduced acid secretion due to CAG has a great effect on the suppression of esophageal mucosal erosion, and, of the various subjective symptoms, acid reflux symptoms are suppressed because gastric acid secretion is markedly low. This might be the reason why the prevalence of NERD among GERD patients changes according to the *H.pylori*-related chronic gastritis groups.

The prevalence of NERD among subjects with total FSSG scores $\geqslant 8$ was higher for *H.pylori*-positive subjects than for their negative counterparts. Groups A-D showed no marked differences in gastrointestinal dysmotility scores, and no marked differences were apparent between *H.pylori*-positive and *H.pylori*-negative subjects or between PG-positive and PG-negative subjects. These findings are extremely important when studying the disease state of GERD. In other words, in Groups C and D, where gastric mucosal atrophy is severely advanced, the symptoms and onset of NERD are influenced by gastrointestinal dysmotility rather than acid reflux, thus affecting therapy planning[6].

At present, the incidence of *H.pylori* infection is decreasing in Japan, and the number of patients with chronic atrophic gastritis or gastric cancer is expected to decrease in the future. However, the number of Group A subjects (*H.pylori*-negative and PG-negative) is likely to increase. Therefore, RE in Group A subjects who may experience both acid reflux and dysmotility symptoms must be managed. In Groups C and D, with a higher risk of gastric cancer[8,30], treatments are provided less frequently for RE, but because acid reflux symptoms are lacking, these subjects are less likely to visit a medical center on their own and undergo thorough testing, such as upper gastrointestinal endoscopy.

Instead of prospectively observing the onset rate of GERD over a long period of time, the present study analyzed GERD-related symptoms and the prevalence of endoscopic RE, based on the stage of *H.pylori*-related chronic gastritis at a single time point when endoscopy and history-taking were performed. A prospective study based on long-term follow-up observation is needed to more accurately assess GERD risks. However, acid reducers, including PPIs, are often prescribed to patients with upper abdominal symptoms, and various therapeutic modifications make such studies difficult to implement. The present study involved a group of workers, consisting of almost all males, who underwent endoscopy as part of regular checkup programs of gastric cancer screening. Thus, since most study subjects were men, this must be taken into account when interpreting the results. The present study clarified that *H.pylori* infection and CAG stage correlate closely with acid reflux and dysmotility symptoms. However, because GERD is a disease that is closely related to diet and lifestyle diseases such as obesity and diabetes[31-33], thorough investigation of the correlations of these factors to upper gastrointestinal symptoms is necessary using a GERD-specific questionnaire. Furthermore, ambulatory esophageal pH (with/without impedance) monitoring was not done in this study, and the term "NERD" might not be appropriate. NERD cases include functional heartburn cases in this study, and this should be taken into consideration when interpreting the data.

In conclusion, the present results suggest that the disease state of GERD was related to the stage of *H.pylori*-related chronic gastritis based on measurements of *H.pylori*-Ab titers and serum PG levels (Figure 1). These two serum markers can be measured conveniently, noninvasively, and relatively inexpensively. The reproducibility of test results is high, and many specimens can be measured at the same time. Like Japan, the prevalence of *H.pylori* infection is high and the development of CAG is closely involved with gastric cancer in East Asian countries, such as China and Korea and in Eastern Europe, and Middle and South America. Conducting serum tests along with

routine endoscopic examination is useful not only for gastric cancer screening, but also to obtain more information about patients with reflux disease.

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COMMENTS

Background

We have classified the progression of Helicobacter pylori (H.pylori)-related chronic gastritis into 4 groups (A-D) on the basis of two serum parameters, H.pylori antibody (H.pylori-Ab) titer and serum pepsinogen (PG) level, as a screening test for extensive chronic atrophic gastritis (CAG), and reported a stepwise increase in the incidence of gastric cancer. In this study, the association of H.pylori-related chronic gastritis progression with upper gastrointestinal symptoms and gastroesophageal reflux disease (GERD) was evaluated, because there are only a few previous studies in which this association has been examined.

Research frontiers

This study can help us to understand the natural history of GERD, as well as other illnesses including gastric cancer.

Innovations and breakthroughs

Conducting serum tests along with routine endoscopic examination is useful for not only gastric cancer screening, but also to obtain more information about patients with GERD.

Applications

A prospective study based on long-term follow-up observation is needed to more accurately assess GERD risks.

Terminology

H.pylori-related chronic gastritis stage: The groups were determined by the results of the 2 serologic tests (H.pylori-Ab and PG). This classification reflects each stage of the serial changes in stomach mucosa induced by chronic H.pylori infection. The H.pylori-free healthy condition corresponds to 2 negative tests (Group A). With the establishment of H.pylori infection, the antibody test becomes positive (Group B). As the infection spreads, the PG test also turns positive (Group C). Group C has extensive CAG. Intestinal metaplasia develops and spreads in the presence of CAG, leading to reduction of the bacterial load in the stomach. This results in a negative specific antibody test (Group D). Thus, Group D comprises those subjects with metaplastic gastritis.

Peer review

This article provides interesting data about H.pylori-Ab and serum PG levels in subjects with GERD. These data are of epidemiological interest and provide some insight into theoretical aspects.

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CASE REPORT

Double balloon enteroscopy to retrieve an accidentally swallowed dental reamer deep in the jejunum

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Abstract

Accidentally swallowed foreign objects are not uncommon but difficult to manage without complications. We describe the case of a 68 year old man who accidentally a swallowed sharp-pointed dental reamer that had reached deep in his jejunum. Double balloon enteroscopic retrieval was performed with polypectomy snare but the reamer was entangled in the wire loop of the snare and penetrated the jejunal wall. After releasing the reamer by pushing and pulling the snare for approximately 30 min, the reamer was retrieved with biopsy forceps. This is the first report of double balloon enteroscopic removal of a dental reamer. Furthermore, this is a novel case with regard to decision making in situations when sharp objects are swallowed.

Key words: Dental reamer; Jejunum; Double balloon enteroscopy; Endoscopic retrieval of sharp objects

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INTRODUCTION

Accidental swallowing of foreign objects is not uncommon and may require emergency medical assistance. However, endoscopic removal of swallowed objects from the small intestine without complications is challenging due to the narrow lumen and long length of this organ. Here we report on the use of double balloon enteroscopy to retrieve an accidentally swallowed dental reamer deep in the jejunum.

CASE REPORT

A 68 year old man was admitted to our hospital for accidental swallowing of a dental reamer. On admission, he showed no abnormality in his laboratory data and general well-being. In the past, he had an operation on his tongue due to cancer. Abdominal radiography and CT scanning revealed a dental reamer in his jejunum and no perforation of the gastrointestinal (GI) wall (Figure 1). Double balloon enteroscopic examination was carried out with anterograde approach and the reamer was located deep in the jejunum. Endoscopic removal of the reamer was attempted using a polypectomy snare. Initially, we tried to hold the tip of the reamer but the reamer became entangled in the wire loop of the snare. The patient spontaneously belched, the endoscope was pulled out to the oral side and the needle of the reamer which was entangled in the snare wire penetrated the jejunal wall (Figure 2A). We tried to free the reamer by pushing and pulling the snare but the reamer

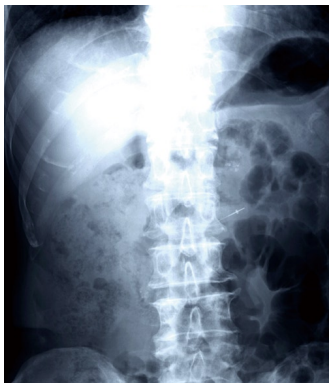

Figure 1 Abdominal radiographs showing dental reamer deep in the jejunum.

did not come off the jejunal wall because the flexible arm of the snare only stretched or bent over. Instead, we tried to push and pull the scope backward towards the oral side, hoping to avoid bending the snare arm. Finally, we released the reamer from the jejunal wall in approximately 30 min. After release of the reamer, we thoroughly examined the penetration site. There was no mucosal lesion. Next, we managed to hole the tip of the reamer needle by using biopsy forceps and removed it from the jejunum without further complications (Figure 2B, C).

DISCUSSION

The majority of foreign bodies which enter the GI tract pass through harmlessly with the feces. The literature shows that 10%-20% of these events require non-surgical intervention and approximately 1% requires surgery[1-3]. However, the guideline for the management of ingested foreign bodies from the American Society for Gastrointestinal Endoscopy indicates that the complications caused by ingestion of sharp-pointed objects are as high as 35%[4]. In the case of the small intestine, complications associated with sharp-pointed objects include ingestion of fish bones[5], pins[6], toothbrush[7], toothpicks[8] and needle[9].

To the best of our knowledge, this is the first report of double balloon enteroscopic removal of a foreign body (dental reamer) from the small intestine. Previously, only one publication in the English language has reported colonoscopic removal of a dental reamer from the colon[10]. In the aforementioned case, the reamer was retrieved by passing a polypectomy snare around the sharp end of the reamer and then the colonoscope was gently withdrawn with the reamer sharp end trailing to avoid injury. In the present case, it took some time to release the reamer from the jejunal wall due to the narrow lumen and long length of the jejunum; contact between the sharp end of the reamer and the jejunal wall was difficult to avoid. Additionally, there was restricted movement and difficulty in manipulating the enteroscope because it had reached deep into the jejunum. Finally, the driving force could not be transmitted to the snare due to the flexibility of the

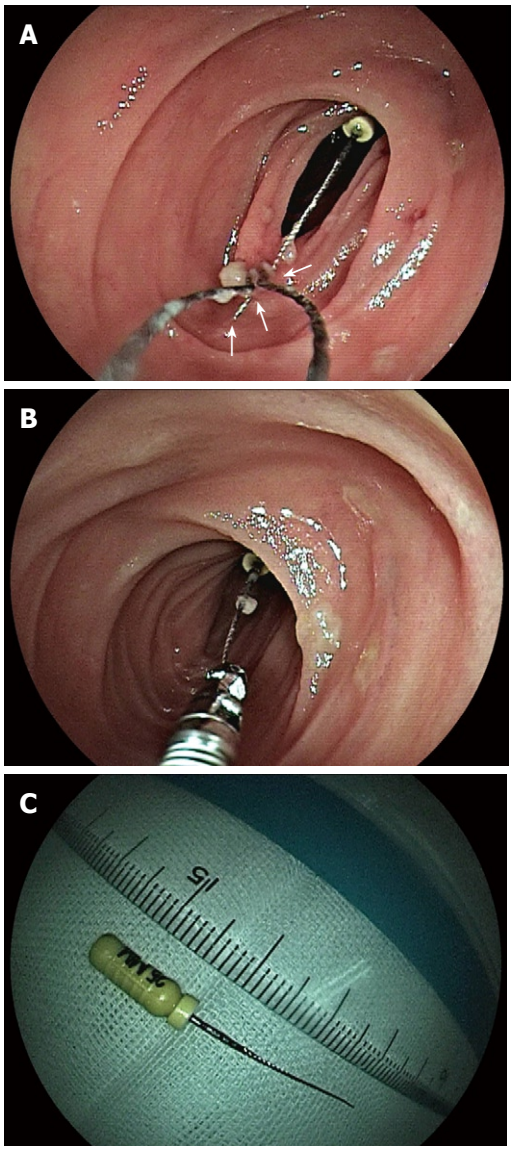

Figure 2 Double balloon enteroscopy showing the dental reamer deep in the jejunum. A: The needle of the reamer which was entangled in the snare wire had penetrated the jejunal wall; Arrow heads show the point of penetration and the free end of the sharp-pointed head; B: The dental reamer was held by an alligator jaw forceps; C: The dental reamer was successfully retrieved by double balloon enteroscopy.

snare arm. We think that enteroscopic removal of foreign objects from the small intestine demands skilful handling of endoscopic instruments as dictated by the long length and narrow lumen of the small intestine. We retrieved a sharp foreign object by a combination of chance and skill. However, this operation was complicated by the anatomy of the organ and carried a high risk of perforation. Another option might have been to retrieve the dental reamer through the overtube together with the endoscope[11]. Another choice is single balloon enteroscopy but this was not available to us in this situation. Single balloon enteroscopy is easy to push and pull the fiberscope through the overtube and the jejunal wall can be protected by pulling sharp-pointed objects into the overtube. Accordingly, our impression is that enteroscopical retrieval of sharp objects

should be *via* the over-tube. Finally, this is a novel case with regard to decision making in a situation when sharp objects are swallowed.

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WJGE World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2011 April 16; 3(4): I
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Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 04-05, 2011
13th Duesseldorf International Endoscopy Symposium
Duesseldorf, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week
Westin Bayshore, Vancouver
British Columbia, Canada

March 03-05, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-19, 2011
41. Kongress der Deutschen Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.
Munich, Germany

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey

April 07-09, 2011
International and Interdisciplinary Conference Excellence in Female Surgery
Florence, Italy

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Stauffenbergstr. 26
Berlin 10785, Germany

April 18-22, 2011
Pediatric Emergency Medicine: Detection, Diagnosis and Developing Treatment Plans
Sarasota, FL 34234, United States

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong
Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

April 28-30, 2011
4th Central European Congress of Surgery
Budapest, Hungary

May 07-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis
London, England, United Kingdom

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV Spigc
II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

September 10-11, 2011
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street
Los Angeles, CA 90015, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel
Brussels 1210, Belgium

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 02, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku
Tokyo 107-0052, Japan

December 01-04, 2011
2011 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical & Research Conference
Hollywood, FL 34234, United States

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253), is a monthly, open-access (OA), peer-reviewed online journal supported by an editorial board of 400 experts in gastrointestinal endoscopy from 45 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGE* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGE* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

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Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and

Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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