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Contents

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Contents

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Use of anesthesia on the rise in gastrointestinal endoscopy

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Abstract

Conscious sedation has been the standard of care for many years for gastrointestinal endoscopic procedures. As procedures have become more complex and lengthy, additional medications became essential for adequate sedation. Often time's deep sedation is required for procedures such as endoscopic retrograde cholangiography which necessitates higher doses of narcotics and benzodiazepines or even use of other medications such as ketamine. Given its pharmacologic properties, propofol was rapidly adopted worldwide to gastrointestinal endoscopy for complex procedures and more recently to routine upper and lower endoscopy. Many studies have shown superiority for both the physician and patient compared to standard sedation. Nevertheless, its use remains highly controversial. A number of studies worldwide show that propofol can be given safely by endoscopists or nurses when well trained. Despite this wealth of data, at many centers its use has been prohibited unless administered by anesthesiology. In this commentary, we review the use of anesthesia support for endoscopy in the United States based on recent data and its implications for gastroenterologists worldwide.

Key words: Propofol; Ketamine; Conscious sedation; Deep sedation; Anesthesiology; Gastrointestinal endoscopy

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INVITED COMMENTARY ON HOT ARTICLES

The fiberoptic endoscope, patented in 1956, has revolutionized the diagnosis and treatment of gastrointestinal disorders[1]. Since its introduction, the indications for use of the gastroscope and colonoscope have grown exponentially, and newer endoscopic tools including the side viewing and double balloon endoscopes with the ability to perform endoscopic therapy have further expanded these indications. According to a national survey of the general population in 2010, 54.6% of Americans underwent colon cancer screening with colonoscopy at least once within the past 10 years[2]. This number is expected to rise further given recent evidence suggesting a 53% reduction in colon cancer mortality from colonoscopy and polypectomy[3]. Additionally, colonoscopy has become the standard diagnostic tool for the investigation of other colonic complaints including rectal bleeding, change in bowel habits, abnormal radiological findings, anemia, and abdominal pain.

Healthcare expenditures in the Unites States have been climbing significantly, and the use of anesthesia services for endoscopy is no exception. In 2010, healthcare costs exceeded $2.6 trillion dollars, which is twice the amount spent in 2000, and ten times the national cost in 1980[4]. In the wake of escalating health care costs, attention at the national level has been given to cost-cutting measures in all healthcare sectors. One area of potential cost-savings is minimizing overuse of medical services. For example, Korenstein *et al*[5] reviewed recent

literature related to the overuse of procedures, tests, and medications between 1978 and 2009. They found evidence of overuse in 18.4%-60.8% of colonoscopies and 5.2%-23.0% of upper endoscopies. Likewise, the burgeoning use of anesthesia support for gastrointestinal procedures has further escalated the overall cost for endoscopy. In this article, we summarize a recent important study that examines the actual trends in sedation utilization across the United States in the past few years reported by Liu *et al*[6] and discuss selected aspects of anesthesia support for endoscopy.

Liu *et al*[6] recently reported on the overall utilization of anesthesia services for gastrointestinal procedures in the United States and assessed temporal changes and geographic patterns. The authors analyzed data from insurance claims paid by medicare and commercial health insurers for services provided between 2003 and 2009. The authors used data from the Medicare Limited Data set which is a nationally representative sample comprised of 5% of the general population. Data about commercial insurers were taken from the MarketScan data set which holds information from approximately 150 commercial health plans, about 40 million commercially insured individuals, who comprise 20% of the population covered by employer-sponsored healthcare plans. They evaluated all patients who underwent outpatient upper and lower endoscopy over the 6 year period. Exclusion criteria included patients younger than 18 years of age and patients with incomplete claims data for the 6 mo prior to the endoscopy. They calculated the number of upper and lower gastrointestinal endoscopies, the proportion of procedures which used anesthesia services, the average and aggregate payments for these services, and the proportion of anesthesia services utilized for patients deemed low-risk for conscious sedation. They defined low-risk patients as those with American Society of Anesthesiologists (ASA) physical status 1 or 2. Patients without an associated ASA physical status classification in the insurance claim were assigned one based on a predictive statistical model. They estimated the patient's likelihood of having an ASA physical status of 3 or higher based on age, gender, comorbid medical conditions, and any inpatient hospitalization within the 3 mo prior to the procedure. Pertinent comorbidity contributing to anesthesia risk included cardiopulmonary conditions such as cardiac arrest, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, asthma, and cystic fibrosis. A number of other additional medical conditions were used as predictors like cerebrovascular disease, hypertension, peripheral artery disease, *etc*.

They found that 26.6% of 1.1 million Medicare patients had anesthesia services billed for either an upper endoscopy or colonoscopy. Of the 5.5 million privately insured patients, about 28.6% of patients had billed for anesthesia services. For medicare patients, the number of procedures per million patients remained steady at 136 718 from 2003 to 2009. While the number of gastrointestinal procedures per million for privately insured patients grew, however, by more than 50% from 33 599 in 2003 to 50 816 in 2009. Over that same time period, the percentage of procedures utilizing anesthesia services for endoscopy rose in both cohorts. The proportion of medicare patients undergoing gastrointestinal endoscopy with anesthesia support grew from 13.5% in 2003 to 30.2% in 2009. Similarly, anesthesia support for procedures among privately insured patients grew from 13.6% to 35.5% in the same time period. Marked geographic variations were also found. The lowest region was the West with 14% of medicare patients and 12.6% of privately insured patients utilizing anesthesia in 2009, while the highest was the Northeast region with 47.5% of medicare patients and 59% of privately insured patients billing for anesthesia services for endoscopy.

The most significant finding in this study was the large number of patients deemed as low-risk who received anesthesia services for their procedures. Overall of the studied patients, approximately two-thirds of the medicare patients with ASA physical status level < 3 and more than three-quarters of commercially insured patients had anesthesia support for their procedures. This represents an almost doubling of the Medicare patients over the course of the study, increasing from 13 989 per 1 million in 2003 to 25 069 per 1 million in 2006. For privately insured patients, the increase was more dramatic rising from 3938 to 15 108 per 1 million patients, representing an almost 4 fold increase.

This study has much strength. It is one of the most exhaustive studies published utilizing a large population of both government and privately insured patients. With a total of 6.6 million patients across the United States, it covers a variety of racial, socioeconomic, and geographic backgrounds. The authors were able to overcome the possible lack of information inherent to studies examining records of specific hospitals because insurance billing information enabled them to evaluate all available records regardless of healthcare system. The major weakness was the definition of high and low risk patients. The basic assumption was that patients with ASA physical status > 2 are at higher risk for complications and would thus benefit from anesthesia services. There are, however, few studies which compare the risk of complications associated with moderate sedation *vs* deep sedation in these particular patient groups although prior studies show a link between cardiopulmonary complications and ASA class with conscious sedation[7]. Secondly, only 14.1% of the study population had ASA physical status documented. As noted above, the investigators used a calculated predictive model for the rest of their population. This mathematical model utilized a number of diagnoses and criteria to determine the patient's risk but provided no evidence to confirm the accuracy of this statistical model. Lastly, this study excluded children under the age of 18, hospitalized patients, patients covered by Medicaid, and those paying out of pocket. These populations, particularly self-paying patients, could alter the percentage of patients necessitating anesthesia services.

The increasing use of anesthesia support by anesthesia specialists for both diagnostic and therapeutic endos-

copy revolves around the use of propofol. Since its introduction in the 1980's, its use has slowly expanded into endoscopic sedation principally because of its pharmacologic properties: it is a very short acting sedative agent without analgesic effect resulting in both sedation and amnesia[8]. A wealth of data including randomized controlled trials has shown that non anesthesiologist administered propofol (NAAP) is both safe and effective[9-14]. This data has been generated worldwide including from Asia[15,16]. For example, randomized trials comparing NAAP to meperidine and midazolam combinations have shown no difference in hypoxemia, bradycardia, or need for airway interventions[9]. Indeed, these studies show the safety of NAAP is comparable to endoscopist administered standard sedation. Most studies do demonstrate NAAP sedation is superior to standard sedation regarding time to sedation as well as speed of recovery. Patient satisfaction with propofol is variable from equivalent to slightly superior to the standard regimens. It should be stressed, however, that the reporting of the use of NAAP comes from centers with much experience in its administration and only after a rigorous training program for administering staff.

Despite this apparent efficacy and safety, the use of propofol by non-anesthesiologists is a highly charged area both in the United States and abroad[17,18]. In the United States, the labeling on propofol states that "it should be administered only by persons trained in the administration of general anesthesia". Recently, the United States Food and Drug Administration denied a change in this labeling thus essentially preventing the use of gastroenterologist administered propofol for endoscopic procedures. Increasingly, anesthesia societies suggest that patients undergoing deep sedation which can occur during endoscopy require a similar level of care to those undergoing general anesthesia[19,20]. More recently, many institutions such as our own have established policies where other agents resulting in deep sedation such as ketamine are being withheld from the gastroenterologists purview thus essentially forcing the use of anesthesia services for complex patients that in the past were safely managed by the gastroenterologist.

For many years, the standard of care for endoscopic procedures was sedation with benzodiazepines and narcotics, referred to as conventional or conscious sedation. However, with the availability of propofol, much literature has been dedicated to the increasing use of propofol and monitored anesthesia care (MAC) sedation in gastrointestinal endoscopy as compared to conventional sedation[21-25]. In addition, many gastroenterologists favor the use of propofol because of more rapid patient recovery and better patient tolerance[21].

Without question, a major reason for the increasing use of NAAP for gastrointestinal procedures is a financial one. Because it provides for quicker sedation, recovery, and discharge, gastroenterologists are able to be more efficient in providing endoscopy to patients. Vargo *et al*[26] showed the gastroenterologists were able to perform three colonoscopies under propofol sedation in the time it takes to perform two colonoscopies with conventional sedation. This significant improvement in efficiency translated into measurable decreases in the operating costs, nurse requirements, and bed requirements in the recovery area. In addition, the payment to anesthesiologists by private insurance as documented by Liu *et al*[6] is another economic driver and perhaps one reason for the increasing interest in performing endoscopic procedures by the anesthesiology community. However, Cohen *et al*[27] postulated that the cost of anesthesia services used for every endoscopic procedure annually could amount to $8 billion per year and other models support this large financial cost[28]. This is based on an average cost of $400 for anesthesia with endoscopy, although this number is somewhat variable. No study to date documents whether the expediency benefits of anesthesia care provides sufficient economic cuts to offset its additional cost if used for all 20 million endoscopic procedures performed annually in the United States.

Although anesthesia administered propofol is increasingly used worldwide, other options for sedation exist but are overlooked and perhaps underused in the general community. One such practice is the use of unsedated procedures[29-31]. Dumortier *et al*[29] studied 1100 patients in 3 institutions in France who underwent unsedated transnasal upper endoscopies. These patients underwent EGD for various indications with either a 5.9 mm or 5.3 mm endoscope. They found the procedure was feasible in 93.9% of patients. In those that failed, the cause was unsuccessful insertion in 62.7% of the times, patient refusal in 19.4% of the times, and pain in 17.9% of the times. Characteristics associated with failure were young age, female sex, and the need for larger endoscopes. A similar study was performed for unsedated colonoscopy. Petrini *et al*[30] performed 2091 colonoscopies between June 6, 2006 and December 7, 2006 in an ambulatory endoscopy center in California. These patients were given the option to have the procedure with or without sedation. 578 patients (27.6%) started without any sedation. Of these patients, 470 (81.1%) completed the exam without any sedation. Cecal intubation rates were similar in the sedated and unsedated groups, 99.1% and 97.4% respectively. Most importantly, about 97.4% of the patient who underwent unsedated colonoscopies were satisfied with their comfort level and would be willing to under go their next colonoscopy without any sedation. The time to cecum in these patients was not significantly different in the sedated and unsedated patients, 9.71 min *vs* 9.87 min respectively. It, however, was significantly different for those who required sedation after the procedure started with a mean cecal intubation time of 15.24 min. This significant delay in time would prevent many gastroenterologists from pursuing this option seriously unless there was some way to predict the patient that would not tolerate unsedated procedures.

It is not yet clear which option best maximizes patient safety, patient and provider satisfaction with the endoscopy experience, and cost saving. The desire to use propofol over benzodiazepines and narcotics is obvious

because it shortens the endoscopy time, while improving the experience for both the patient and the endoscopist. The use of an anesthesiologist for more complicated procedures is intuitive particularly in those with significant comorbidity (ASA Class 4 or greater) or risk factors for complications. However, we previously found that even in these patients the use of standard conscious sedation supplemented with low dose ketamine was highly effective and safe[32] and such a sedative cocktail may be of benefit in regions of the world where an anesthesiologist is not available. Certainly the lack of formal training in the use of sedatives in gastrointestinal fellowship does affect the practices of gastroenterologists in the community. Thus the utilization of anesthesia services for MAC and propofol may stem from lack of experience with the use of sedatives such as propofol or the desire to avoid the legal liability it involves. It also allows the endoscopist to abdicate the responsibility of sedation and monitoring to another trained medical staff, allowing them to focus on the endoscopy solely. That being said, the most recent recommendations from the ASGE standards of practice committee in 2008[33] suggest that the use of anesthesia services for MAC or propofol sedation in gastrointestinal endoscopy is indicated only for patients undergoing prolonged or therapeutic endoscopic procedures that require deep sedation, patients with anticipated intolerance to conventional sedation, patients with severe comorbidities (ASA physical status class Ⅲ or higher), and patients with higher risk of airway obstruction due to some anatomical variant. Similar guidelines have been published by the American Society of Anesthesiologists Task Force[34].

In addition to the discussion regarding sedation, technical factors may play a role in the decision to use conscious sedation *vs* propofol-based sedation. Methods to reduce discomfort during endoscopy, principally colonoscopy, such as the use of carbon dioxide insufflation[35], water aided colonoscopy[36] as well as an ultrathin colonoscopy[37,38].

More studies are needed to prove improved safety or decrease in healthcare costs before anesthesia can become the new standard for endoscopic procedures. However the "cat may be out of the bag" given the widespread use of propofol, the increasing pressure from consumers, the burgeoning use of narcotics and other medications making conscious sedation more difficult, and stringent regulations on the use of drugs such as ketamine and propofol by the government and anesthesia societies.

Ultimately, the decision to use conscious sedation, nurse-administered propofol sedation, or anesthesia provided propofol will be dictated by the expertise of the physician and the local environment. In areas of the world where the use of NAPS and ketamine are not restricted, these could be used more liberally with the assurance that the providers are well experienced in the pharmacology of the medications and rescue. Ketamine is a wonderful addition to conscious sedation and should be used more. At our institution, however, despite our experience with using ketamine and its remarkable safety, we are now limited by our hospital policy such that we cannot provide deep sedation and must rely on anesthesia support for difficult to sedate patients. Like much we do in medicine, sedation for endoscopic procedures is an art.

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MINIREVIEWS

Diagnosis and management of gastric antral vascular ectasia

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Abstract

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal upper GI haemorrhage. The diagnosis is mainly based on endoscopic pattern and, for uncertain cases, on histology. GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused-way, the so called honeycomb stomach. The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria. The main differential diagnosis is with Portal Hypertensive Gastropathy, that can frequently co-exists, since about 30% of patients with GAVE co-present a liver cirrhosis. Autoimmune disorders, mainly represented by Reynaud's phenomenon and sclerodactyly, are co-present in about 60% of patients with GAVE; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis and systemic sclerosis. In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure, bone marrow transplantation and cardiac diseases. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoural and autoimmune factors and hemodynamic alterations. In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices. Medical therapy has not clearly shown satisfactory results and surgery should only be considered for refractory severe cases, since this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Endoscopic therapy, particularly treatment with Argon Plasma Coagulation, has shown to be as effective and also safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

Key words: Gastric antral vascular ectasia; Bleeding; Watermelon stomach; Argon plasma coagulation

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INTRODUCTION

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal up-

per GI hemorrhage[1]. This disease was first described in 1953 by Ryder *et al*[2], but deeply investigated only 25 years later, in 1978, by Van Vliet *et al*[3]. Since then, a better but still incomplete knowledge of this condition has been reach; however, the exact prevalence is not known, the pathogenesis remains unclear and the best therapeutic approach has not yet been defined. The aim of this paper is to review the current findings about GAVE and to contribute to a better understanding of this often misdiagnosed disease and critically review the current therapeutics options.

MORPHOLOGICAL ASPECTS

GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused-way, the so called honeycomb stomach[4] (Figures 1 and 2).

GAVE is typically located in the gastric antrum, however it may be rarely found also in other areas of the GI tract, including cardia[5,6], duodenum, jejunum[7] and rectum[8,9]. The involvement of the proximal part of the stomach is almost rare and generally located within a diaphragmatic hernia[10]. At the endoscopic ultrasound (EUS), the gastric antrum appears hyperthrophic with a spongy appearance of the mucosa and submucosa and a well-preserved muscularis propria[11,12].

The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation (= smooth muscle cell and myofibroblast hyperplasia) and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria[13-15] (Figures 3 and 4). In 1989, Gilliam *et al*[14] proposed a score system to diagnose GAVE, which considered only two histological criteria: the co-presence of ectasia and/or fibrin thrombi and spindle cell proliferation (Gilliam's score). Subsequently, a third parameter, fibrohyalinosis, was added to improve both sensibility and specificity[15]. This latter score, called "GAVE score", showed a higher diagnostic accuracy (80%) to differentiate GAVE from Portal Hypertensive Gastropathy, which may be present in patients with co-existing portal hypertension. Table 1 summarized both the histological scores, the Gilliam's score and the GAVE score.

GAVE *VS* PORTAL HYPERTENSIVE GASTROPATHY: DIFFERENTIAL DIAGNOSIS

Patients with portal hypertension often present an endoscopic pattern called portal hypertensive gastropathy (PHG), which needs to be distinct from the GAVE pattern, since they represent two separate entities in the setting of liver cirrhosis. The differential diagnosis is mainly based on the endoscopic appearance and, in the doubtful cases, by the histological pattern.

PHG occurs only in patients with portal hypertension and typically involves the fundus and the corpus of the stomach; the endoscopic pattern is characterized by a combination of four main characteristics: a mosaic-like pattern, presence of red point lesions, cherry red spots and black-brown spots[16]. The histological findings may clarify the uncertain cases by the assessment of the "GAVE score", indeed, a GAVE score > 3 is considered highly diagnostic for the presence of GAVE (Table 1)[15].

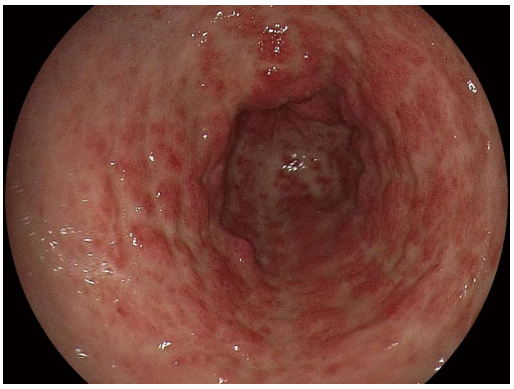

Figure 1 Endoscopic appearance of gastric antral vascular ectasia: Red spots radially departing from pylorus and involving the gastric antrum.

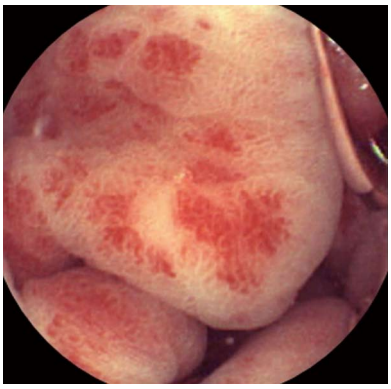

Figure 2 Videocapsule image of gastric antral vascular ectasia.

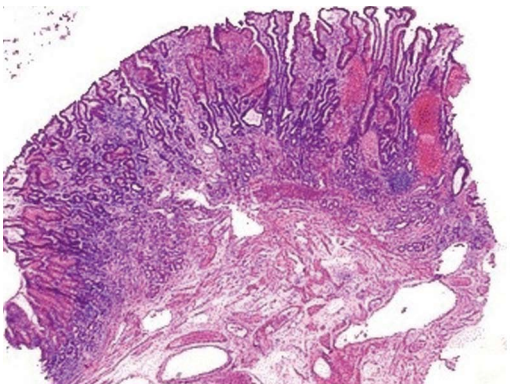

Figure 3 Gastric biopsy showing prominent vascular congestion with thrombosis of the vasculature. The surrounding glands appear regenerative and the vessels in the submucosa are dilated and sclerotic.

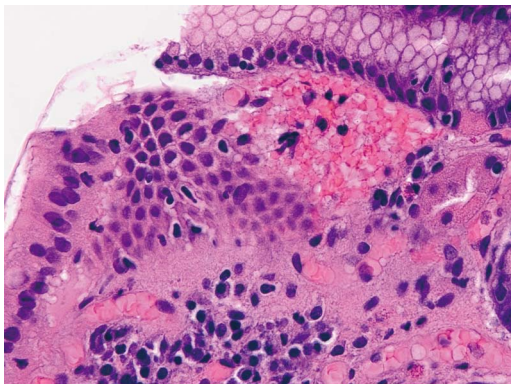

Figure 4 Higher magnification of one of the thrombosed vessels.

Table 1 Histological score systems for diagnosis of gastric antral vascular ectasia

	Gastric antral vascular ectasia score (range 0-5)		Gilliam's score (range 0-4)
Score	Fibrin thrombi and/or vascular ectasia	Spindle cell proliferation	Fibrohyalinosis
0	Both absent	Absent	Absent
1	One present	Increased	Present
2	Both present	Marked increased	-

The main aspects to consider in the differential diagnosis between GAVE and PHG are summarised in Table 2. The importance to distinguish these two clinical entities is mainly related to the different therapeutic approach; the reduction of portal pressure by using drugs (beta-blockers, somatostatin, octreotide), trans-jugular intra-hepatic porto-systemic shunt (TIPS) or surgery (portocaval shunts) are not effective for the treatment of GAVE[17,18].

GAVE AND ASSOCIATED DISEASES

GAVE syndrome can complicate the course of many diseases (Table 3). Autoimmune disorders, mainly represented by Reynaud's phenomenon and sclerodactyly, are co-present in about 60% of patients with GAVE[10]; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome[19], systemic lupus erythematosus[20], primary biliary cirrhosis and systemic sclerosis[21]. In this latter case, it has been reported that GAVE can even represent the presenting syndrome, preceding the development of the autoimmune disorders by several months[21].

About 30% of patients with GAVE co-present a liver cirrhosis[22-24], whatever etiology (viral, autoimmune, toxic-metabolic). In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure[10], bone marrow transplantation[25] and cardiac diseases[10,26].

Non-cirrhotic patients more frequently present the typical endoscopic watermelon-, striped-pattern and are mainly represented by middle-aged women whereas the honeycomb-, diffuse-pattern prevails in patients with liver failure[1,4,27]. However, the endoscopic appearance is not related to the patient's outcome[4] but could reflect a different pathogenesis.

Table 2 Differential diagnosis between portal hypertensive gastropathy and gastric antral vascular ectasia

Features	Portal hypertensive gastropathy	Gastric antral vascular ectasia
Site	Fundus-corpus	Antrum
Endoscopic pattern	Combination of: Mosaic-like pattern Red point lesions Cherry red spots Black-brown spots	Red spots organised: Striped-pattern (watermelon-stomach) Diffused-pattern (honeycomb-stomach)
Histological pattern	Not specific	Highly specific
Response to β-Blockers/transjugular intrahepatic portosystemic shunt/portocaval shunts	Present	Absent

Table 3 Gastric antral vascular ectasia and associated diseases

Associated disease	Prevalence (%)	Ref.
Autoimmune diseases	60	
Raynaud's phenomenon		[10]
Sclerodactyly		[10]
Sjogren's syndrome		[19]
Systemic sclerosis		[21,32]
Primary biliary cirrhosis		[10,32]
Systemic lupus erythematosus		[20]
Liver cirrhosis and/or portal hypertension	30	[22-24]
Others	10	
Chronic renal failure		[10]
Bone marrow transplantation		[25]
Cardiac diseases		[10,26]

PATHOGENESIS

GAVE syndrome is an acquired disease rather than a congenital alteration. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoural and autoimmune factors and hemodynamic alterations.

Mechanical stress represented by strong gastric peristalsis has been supposed to induce prolapse and trauma of antral mucosa and intermittent obstruction of blood vessels, which can lead to fibro-muscular hyperplasia and vascular ectasia[28]. These latter are typical findings of GAVE and other gastrointestinal lesions due to repeated traumas and mucosal prolapse (i.e., stomas and prolapsed haemorrhoids)[13]. Furthermore, a subset of patients with liver cirrhosis and GAVE has been showen to have antro-pyloric dysfunction with abnormal antral motor response to meals[29].

Many authors have assumed a pivotal role of humoral factors as gastrin, vasoactive inhibitory peptide (VIP), 5-hydroxytryptamine, glucagon, catecholamines, prostanoid and other undefined vasoactive substances. GAVE syndrome has been associated with both increased[28] and decreased levels of gastrinemia[15] and these conflicting data reduced the importance initially ascribed to this

hormone, which was hypothesised to induce spindle cell proliferation, hyperplasia, prolonged sphincter relaxation and also capillary and venous dilatation. A possible role of both VIP and 5-hydroxytryptamine has been proposed after the evidence of the presence of actively proliferating neuroendocrine cells surrounding the ectasic vessels in the lamina propria of patients with GAVE[30]. The release of these substances seems to be responsible for the local vasodilatation and the tendency to bleed. On the other hand, glucagon and catecholamines do not seem to play any role in the pathogenesis of GAVE, since concentrations of these metabolites have shown to be similar in cirrhotics with or without GAVE. However, prostaglandin E2, a prostanoid with vaso-dilatator and acid-inhibitory effect, showed significantly higher levels in patients with GAVE[31].

Up to 60% of patients with GAVE have also an autoimmune associated disease and show the presence of autoantibodies[10], therefore an autoimmune pathogenesis has been suggested. Indeed, several autoantibodies have been detected in patients with GAVE; Watson *et al*[32] found that all patients with systemic sclerosis and GAVE were positive for antinuclear antibodies and, in some cases, were also positive for anti-centromere antibodys. This antibody was subsequently demonstrated to recognize a specific and formerly unknown centromeric protein, involved in the cell growth process[33]. Garcia *et al*[34] and Valdez *et al*[35] found in the sera of a patients with GAVE an antinucleolar antibody that specifically recognized a RNA helicase II (RH-II). It has been speculated that these autoantibodies could cross-react with specific proteins present in the vessels of the gastric mucosa and sub-mucosa inducing the typical alterations. However, the exact role played by these autoantibodies is still unknown and only the development of an animal model will probably provide further information.

It is now evident that portal hypertension does not play a role in the GAVE development, since it is not present in up to 70% of patients, and the reduction of portal hypertension does not affect the course of the disease[17]. Moreover, it has been shown that liver transplantation despite persistent portal hypertension induces complete disappearance of the antral vascular lesions[36]. It could be speculated that liver failure, at least in a subset of patients, and not portal hypertension, could have a role in the pathogenesis of GAVE altering the metabolism of not yet identified substances.

Finally, GAVE syndrome could have a multifactorial pathogenesis, with the driven process strictly related to the different clinical settings (i.e., autoimmune or liver failure setting), thus explaining the dissimilar endoscopic appearance (watermelon- or honeycomb-pattern).

THERAPEUTIC OPTIONS

In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices and the best approach is still to be defined.

Surgery

The surgical approach, most commonly represented by antrectomy**,** has a clear clinical efficacy in the management of GAVE-related bleeding, since none of the patients surgically treated has recurrence of bleeding in the post-operative period[37]. However, this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Novitsky *et al*[37] reviewed 45 reported surgical cases and found that antrectomy was the most frequently performed surgical approach (89% of cases) with a 30-d mortality rate of 6.6% and the principal cause of death was multiorgan failure. As previously mentioned, portocaval shunts, including TIPS, have no role in the treatment of GAVE syndrome[17].

Medical therapy

A wide variety of drugs have been used to try to control GAVE-related bleeding, however no one has clearly shown satisfactory results in order to consider medical therapy as a valid alternative to an invasive approach.

Hormonal therapy - estrogen-progesterone - has been shown to control bleeding related to GI vascular malformations, including GAVE, by undefined mechanisms[38,39]. However, since the vascular lesions persist despite cessation of bleeding, a dose-reduction is usually related to bleeding relapse[40-42]. Moreover, the long-term treatment with hormonal-therapy can induce severe side effects, such as menorrhagia and gynaecomastia, and increase the risk of endometrial and breast cancer[43].

Octreotide, a long-acting somatostatin analogue, has been shown to effectively control chronic bleeding related to vascular abnormalities. Nardone and co-workers treated 3 patients with GAVE-related bleeding with octreotide (0.1 mg subcutaneous three times a day) for 6 mo, obtaining a transient reduction of bleeding in one case and cessation in the others two patients, with partial and total regression of the lesions[44]. This result can be partly explained by several effects exerted by this hormone such as the inhibitory effect on both neuroendocrine cells surrounding the ectatic vessels and on smooth muscle cells, and the anti-angiogenic effect. However, other authors have not confirmed these results[45] and the role played by octreotide needs to be further investigated in larger sample size studies.

Few case-reports have suggested a potential benefit from the use of tranexamic acid but reported severe side effects (central venous stasis retinopathy; deep venous thrombosis and pulmonary embolism) limit its use[46-48].

A case-report showed complete resolution of GAVE with intravenous infusion of methylprednisolone and cyclophosfamide in a patient with associated systemic sclerosis and pernicious anaemia[49]; but, such result has not been yet confirmed in larger series.

In conclusion, drug therapies have no definite role in the cure of GAVE-related bleeding and should be considered an experimental therapeutic approach in the setting of controlled clinical trials.

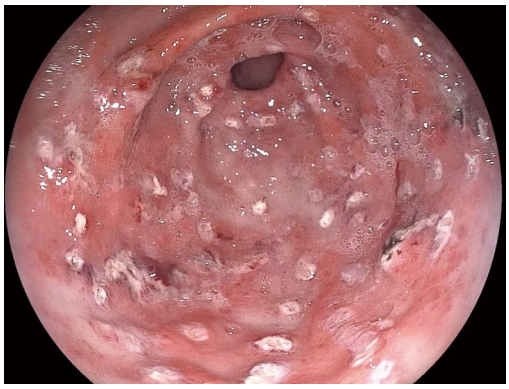

Figure 5 Argon plasma coagulation treatment of gastric antral vascular ectasia in patient with transfusion-dependent anaemia.

Endoscopic treatment

The endoscopic treatment principally represented by laser photoablation and, more recently, by Argon Plasma Coagulation (APC) has shown a similar and safer effect as surgery.

Neodymium-yttrium-aluminum garnet (Nd: YAG) laser coagulation has been successfully used to control GAVE-related bleeding. All series have confirmed the efficacy of this endoscopic thermal therapy by reducing or abolishing the need of blood transfusions in about 50% to 80% of cases, with a mean of 3 treatment sessions (range 1-10)[50-53].

The most serious complication described after laser therapy, even if rare, is represented by gastric perforation. Two weeks after almost all laser therapy sessions, a gastric ulceration is frequently observed, even when the laser treatment session has been performed with an energy power sufficient to induce only superficial scarring without deep tissue necrosis[54]. Another complication observed after repeated treatment sessions, is pyloric stenosis, that can induce either delayed gastric emptying or true obstruction[54,55]. Up to 8% of patients developed this complication, that can be resolved by balloon dilation[55]. Moreover, after multiple, high energy, laser therapy sessions, patients may develop hyperplastic polyps, even after 20 mo of follow-up[56]. These polyps can reach large dimensions and induce recurrent anaemia without evidence of recurrence of vascular abnormalities[56]. Their development is thought to be secondary to reactive foveolar hyperplasia and no focal malignancy has been detected. However, Bernstein and co-workers presented a case-report of a multifocal gastric cancer developed after repeated sessions of laser therapy over a five-year period[57].

Other important disadvantages of laser endoscopic therapy are the high cost and the need of a long training period, since most severe complications, such as perforation and death, happen more frequently when the endoscopist is not sufficiently skilled with the procedure[51,54].

Argon plasma coagulation (APC) is a noncontact technique with a controllable depth of coagulation (0.5-3 mm). High-frequency current is applied to the tissue through ionized and electrically conductive gas, called argon plasma; the diverging gas flow allows an axial, radial and retrograde application (Figure 5). In comparison to Nd: YAG laser therapy, APC is easier to use, more manageable, cheaper and, most importantly, safer; nevertheless, randomized trials comparing the two endoscopic procedures are lacking.

The complications are rare and mostly mild. The most frequently reported complication is represented by intestinal gas distension related to argon flow, which can leave the patient with a feeling of discomfort after the endoscopic session. Wall emphysema and intestinal pneumatosis have been described, but these conditions are usually reversible[58]. More serious adverse events described after APC treatment are asymptomatic antral stenosis[59] and upper GI hemorrhage. One severe case of sepsis, which conduced to death due to infectious peritonitis, has also been described[60]. The risk of intestinal perforation is very low and limited to very thin-walled structures (i.e., caecum)[58,61]; notably, no case of perforation during APC treatment of GAVE has been described.

The largest case series of APC treatment reported an efficacy ranging from 90%[60] to 100%[62], with no further need for blood transfusions and an increase of hemoglobin level from 2.3 g/dL[62] to 5.5 g/dL[58] in almost all patients. The setting of argon gas flow usually ranges between 0.8 L/min and 2.5 L/min, the electrical power from 40 W to 100 W and, generally, a mean of 2.5 sessions are needed to achieve complete eradication[58,62,63].

Several other endoscopic therapies have been proposed in the last years, such as cryotherapy, band ligation and radiofrequency ablation.

A small, prospective pilot study, based on 12 patients, investigated the efficacy of cryotherapy for the treatment of GAVE-related bleeding achieving a complete response to treatment (i.e., no need for blood transfusion) in 50% of cases[64]. Cryotherapy is based on the rapid decrease of temperature due to the rapid expansion of carbon dioxide (CO_2) released by the spray catheter; such sudden decrease of temperature causes superficial necrosis of the mucosa and of the superficial submucosal, with eradication of antral teleangiectasias, and subsequent re-epithelialization. The need for specialized equipment and for specific training, represents Cryotherapy's main limitations; furthermore, the need of an overtube placed to enable passive venting of CO_2, might add technical difficulty and risk to the procedure.

Several case-reports and one observational comparative study have reported the use of band ligation for patients with GAVE related bleeding[65-67]. Based on the small, retrospective study that compared endoscopic band ligation with endoscopic thermal therapy, band ligation showed a significant higher rate of bleeding cessation, fewer treatment sessions required to achieve cessation of bleeding, a greater increase in hemoglobin values and reduction of the need for transfusions[67]. The higher efficacy compared to standard thermal therapy is probably due to a more reliable eradication of the abnormal

vasculature in the mucosa and submucosal.

Finally, a pilot study has investigated the role of radiofrequency ablation for the treatment of GAVE[68]; 6 patients with transfusion-dependent GAVE-related bleeding were enrolled and after 1 to 3 treatments, all but one no longer needed transfusions during the 6 mo follow up, without reporting adverse events.

Although cryotherapy, endoscopic band ligation and radiofrequency ablation have provided encouraging results, well-performed, larger, prospective studies are needed before providing any definitive conclusion.

CONCLUSION

GAVE is an infrequent but severe cause of upper gastrointestinal bleeding, characterized by a pathognomonic endoscopic pattern of red spots organized either in stripes or randomly distributed in the gastric antrum. GAVE can develop in the setting of many diseases, mainly represented by autoimmune diseases and liver cirrhosis. Although many hypotheses, such as mechanical stress, humoral/immunological factors and haemodynamics alterations, have been proposed, the pathogenesis of GAVE remains still obscure and probably different pathways occur in different clinical settings. The therapy is limited to surgical or endoscopic approach, since most drug therapies have shown conflicting results. Surgery has the advantage to be a definitive therapy but with high morbidity and mortality risks, especially in patients with severe co-morbidities, such as liver cirrhosis. Endoscopic therapy, particularly treatment with APC, has shown to be as effective and also a safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

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MINIREVIEWS

Percutaneous endoscopic gastrostomy tube replacement: A simple procedure?

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Abstract

Replacement of gastrostomy tube in patients undergoing percutaneous endoscopic gastrostomy (PEG) is generally considered as a safe and simple procedure. However, it could be associated with serious complications, such as gastrocutaneous tract disruption and intraperitoneal tube placement, which may lead to chemical peritonitis and even death. When PEG tube needs a replacement (e.g., occlusion or breakage of the tube), clinicians must realize that the gastrocutaneous tract of PEG is more friable than that of surgical gastrostomy because there is no suture fixation between gastric wall and abdominal wall in PEG. In general, the tract of PEG begins to mature in 1-2 wk after placement and it is well formed in 4-6 wk. However, this process could take a longer period of time in some patients. Accordingly, this article describes three major principles of a safe PEG tube replacement: (1) good control of the replacement tube along the well-formed gastrocutaneous tract; (2) minimal insertion force during the replacement, and, most importantly; and (3) reliable methods for the confirmation of intragastric tube insertion. In addition, the management of patients with suspected intraperitoneal tube placement (e.g., patients having abdominal pain or signs of peritonitis immediately after PEG tube replacement or shortly after tube feeding was resumed) is discussed. If prompt investigation confirms the intraperitoneal tube placement, surgical intervention is usually required. This article also highlights the fact that each institute should have an optimal protocol for PEG tube replacement to prevent, or to minimize, such serious complications. Meanwhile, clinicians should be aware of these potential complications, particularly if there are any difficulties during the gastrostomy tube replacement.

Key words: Percutaneous endoscopic gastrostomy; Gastrostomy tube replacement; Gastrostomy tube exchange; Gastrostomy tube reinsertion; Complication; Peritonitis; Prevention; Management

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INTRODUCTION

Gastrostomy is indicated when an individual requires long-term prepyloric feeding[1-5]. With an advent of endoscopic procedure, percutaneous endoscopic gastrostomy (PEG) has become more preferential than open gastrostomy thanks to its less invasiveness and better cost-effectiveness[6-11]. Moreover, PEG was associated with significantly faster time to start feeding[12,13]. A PEG tube is usually made of silicone or polyurethane[14-18]; thereby making it very durable and less likely to be damaged by gastric secretion compared to a latex tube[19]. In general, the tract of PEG begins to mature in 1-2 wk after placement and it is well formed in 4-6 wk[20,21]. However, this process

could take a longer period of time in patients with severe malnutrition, immunosuppression, or ascites[22-26]. If a PEG tube is dislodged within a month after placement, it is advised that a repeat endoscopy be performed to replace the tube since the stomach may not well adhere to the abdominal wall, thus resulting in a free perforation[27-29]. Blindly replacing a new tube in this scenario could cause intraperitoneal placement and consequent peritonitis[30].

When PEG tube needs a replacement (e.g., occlusion or breakage of the tube[31-34], or accidental dislodgement of PEG tube[35-37]), clinicians must realize that the gastrocutaneous tract of PEG is more friable than that of surgical gastrostomy because there is no suture fixation between gastric wall and abdominal wall in PEG. Although the incidence of intraperitoneal tube placement in patients with mature gastrocutaneous tract (PEG performed > 30 d) remains unknown, peritonitis after PEG tube replacement has been reported sporadically and it was associated with significant morbidity and mortality[38-46].

PRINCIPLES OF GASTROSTOMY TUBE REPLACEMENT

Although there is no guideline or consensus regarding PEG replacement protocols[47-54], the principles of any PEG tube replacement should include (1) good control of the replacement tube along the well-formed gastrocutaneous tract; (2) minimal insertion force during the replacement, and, most importantly; and (3) reliable method for the confirmation of intragastric tube insertion. Replacing a new tube along the proper tract can be achieved by using a leveler to measure the depth and direction of the tract, exchanging a PEG tube over a relatively short guide wire with or without the assistance of fluoroscopy (the railroad technique, or the modification of Seldinger technique)[55-60], or inserting a new tube under a direct endoscopic view[61,62]. Replacing an old PEG tube with a balloon-tip tube, rather than a mushroom-tip tube or a disc-tip tube, may minimize the risk of gastrocutaneous tract disruption[63-66]. Additional caution should be devoted when replacing PEG tubes in individuals who have non-straight gastrocutaneous tract, who have narrow stoma site, and who have less co-operation.

There are several ways to confirm a proper PEG tube replacement such as aspirating gastric or bilious fluid from the tube, listening to a gurgling sound when flushing air through the replacement tube, and performing a water/saline irrigation test (no resistance or pain when filling the tube with sterile water/saline). These methods are simple but somehow unreliable to indicate whether or not the tube insertion is getting into the stomach. The gold standard to confirm tube position is however to obtain a water-soluble contrast examination through the replacement tube[67-69], or to visualize the internal bolster or balloon *via* an upper gastrointestinal endoscopy[70].

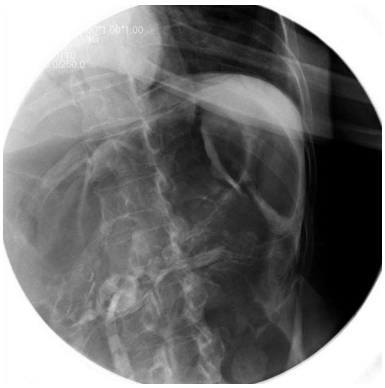

Figure 1 Patient (A 60-year-old woman) developed sudden abdominal pain immediately after percutaneous endoscopic gastrostomy tube replacement. Fluoroscopy of the upper abdomen demonstrated the leakage of water-soluble contrast from a disc-tip gastrostomy tube into the peritoneal cavity (figure courtesy of Dr. Asada Methasate and Dr. Cherdsak Iramaneerat).

STEPWISE APPROACH TO PATIENTS WITH SUSPECTED INTRAPERITONEAL TUBE PLACEMENT

When intraperitoneal tube placement is suspected (e.g., patients having abdominal pain or signs of peritonitis immediately after PEG tube replacement or shortly after tube feeding was resumed), prompt investigation should be performed, either with a water soluble contrast study (Figure 1) or computed tomography scan of the abdomen[41], and tube feeding must be discontinued immediately. In case this situation occurs in an endoscopy room, gastroscopy may show an absence of PEG tube in the stomach which confirms the malposition of gastrostomy tube.

If the investigation reveals gastrostomy tube located in the peritoneal cavity, surgical intervention is usually required such as an exploratory laparotomy with peritoneal lavage for chemical peritonitis (Figure 2). The initial site of gastrostomy may be reused, or closed and a new gastrostomy site be created distal to the former one. Broad-spectrum antibiotics should be given intravenously until clinical grounds and laboratory parameters of infection/inflammation return to normal, mostly within 5-7 d. In a lesser extent of the consequence (i.e., a stable patient with minimal symptoms and signs of peritonitis), non-operative management may be justified[41]. This conservative approach includes the removal of the gastrostomy tube, nasogastric tube decompression, intravenous administration of broad-spectrum antibiotics, and close monitoring of hemodynamic and abdominal signs. A new PEG tube may be placed by endoscopy at a new site in the stomach whenever the patient is completely stabilized.

CONCLUSION

This article emphasizes the potential serious complication for PEG tube replacement, an intraperitoneal placement

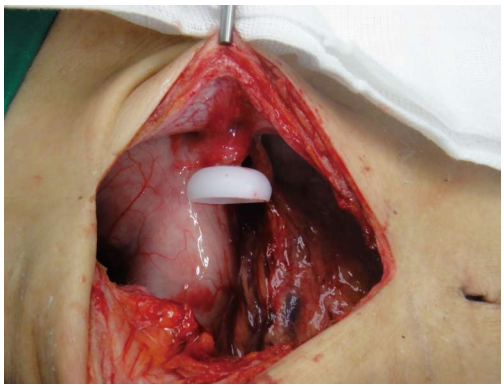

Figure 2 Intraoperative findings of the aforementioned patient showed an intraperitoneal gastrostomy tube, and the separation of mature gastrocutaneous tract close to the stomach (figure courtesy of Dr. Asada Methasate and Dr. Cherdsak Iramaneerat).

and its subsequent peritonitis, which could be associated with significant morbidity and even mortality. Each institute should have an optimal protocol for PEG tube replacement to prevent, or to minimize, such a serious complication. Meanwhile, clinicians should be aware of this complication, particularly if there are any difficulties during the gastrostomy tube replacement.

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REVIEW

Endoscopic management of chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a common gastrointestinal illness, which affects the quality of life with substantial morbidity and mortality. The management includes medical, endoscopic and surgical approaches with the need for interaction between various specialties, calling for a concerted multidisciplinary approach. However, at the time of this publication, guidelines to establish care of these patients are lacking. This review provides the reader with a comprehensive overview of the studies summarizing the various treatment options available, including medical, surgical and endoscopic options. In addition, technological advances such as endoscopic retrograde cholangiopancreatogrophy, endoscopic shock wave lithotripsy and endoscopic ultrasound can now be offered with reasonable success for pancreatic decompression, stricture dilatation with stent placement, stone fragmentation, pseudocyst drainage, and other endoscopic interventions such as celiac plexus block for pain relief. We emphasize the endoscopic options in this review, and attempt to extract the most up to date information from the current literature. The treatment of CP and its complications are discussed extensively. Complications such as biliary strictures. pancreatic pseudocysts, and chronic pain are common issues that arise as long-term complications of CP. These often require endoscopic or surgical management and possibly a combination of approaches, however choosing amongst the various therapeutic and palliative modalities while weighing the risks and benefits, makes the management of CP challenging. Treatment goals should be not just to control symptoms but also to prevent disease progression. Our aim in this paper is to advocate and emphasize an evidence based approach for the management of CP and associated long term complications.

Key words: Chronic Pancreatitis; Biliary strictures; Pseudocysts; Endoscopic management; Pain; Pancreatic stones

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INTRODUCTION

Chronic pancreatitis (CP) is debilitating illnesses, with a prevalence estimated between 4% to 5%[1]. The chronicity of CP and the frequent acute exacerbations significantly impact patients' quality of life. Alcohol is the most common etiology of CP in the western world. Sarles *et al*[2] reported that 60% to 70% of patients with CP have a 6 to 12 year history of alcohol abuse. Other common etiologies of CP include autoimmune pancreatitis, hypercalcemia, as well as idiopathic CP[3].

CP is characterized by irreversible damage that leads to fibrosis and necrosis of the pancreatic tissue[4]. This

destruction of the pancreatic tissue manifests as abdominal pain, the most common presenting symptom of CP[5-9]. Steatorrhea and diabetes are other common presenting symptoms seen with the loss of endocrine and exocrine function of the pancreas[10]. Medical, endoscopic and surgical methods are available for management of CP. Medical management revolves around pain medications, fluid hydration and pancreatic enzyme supplementation surgery seem to be efficacious, at least in the short and mid term but is associated with high morbidity and mortality[11-13]. Technological advances such as endoscopic retrograde cholangiopancreatogrophy (ERCP), endoscopic shock wave lithotripsy (ESWL) and endoscopic ultrasound (EUS) can now be offered with reasonable success for pseudocyst drainage, stricture dilatation with stent placement, and other endoscopic interventions such as celiac plexus block or neurolysis for pain relief[14]. However, choosing amongst the various therapeutic and palliative modalities while weighing the risks and benefits, makes the management of CP challenging.

This review is focused on the current management of CP with emphasis on pain control and treatment of complications. We aim to provide the reader with the most up-to-date evidence on endoscopic modalities available for CP.

MANAGEMENT OF CP

Pain is the most common presenting symptom of CP, and ranges from mild discomfort to severe pain that often requires hospitalization. The origin of pain is much debated; and the consensus at this time is that the etiology of pain is multifactorial[4,15-17]. It can be caused by pancreatic duct obstruction, which subsequently leads to ductal hypertension[9]. Pancreatic duct obstruction can be frequently caused by complications of CP such as pancreatic duct strictures, pseudocysts, intraductal stones, and sphincter stenosis[9].

Medical management

Alcohol abuse is the most common cause of CP in the United States, and the association of binge drinking with acute exacerbation of abdominal pain in CP is well known. Therefore emphasis on alcohol cessation with offering resources on alcohol cessation such as support groups is the first step to manage CP. In addition to alcohol, smoking has also been shown to be an independent risk factor for both acute and CP[18], and smoking cessation is equally important in patients with CP. If the avoidance of exacerbating factors fails to control flare-up of abdominal pain, pain medications should be considered for symptom relief.

Acetaminophen and non-steroidal anti-inflammatory agents should be used for pain relief, if there are no contraindications. Narcotics should never be the first line for control of pain and offering narcotics as first line of pain medication poses a real risk of addiction[16]. Pancreatic enzymes and antioxidants have also been shown to relieve pain in CP. Isakson and co-workers showed a 30% reduction in pain after treatment with oral enzyme preparations in a small number of patients with CP[19]. The mechanism through which enzymatic preparations work is presumed to be *via* a negative feedback pathway involving the pancreas, specifically involving the cholecystokinin pathway[20]. In recent years, this theory has been challenged by conflicting evidence[21].

It is well documented that in CP there is a decreased absorption of vitamins and minerals[22]. Deficiencies lead to increase in oxygen free radicals. There is some data to suggest that removal of oxygen free radicals may have an increased therapeutic effect in controlling pain[23].

Endoscopic management

Advances in understanding the pathogenesis of CP combined with progress in technology have led to an emerging role of endoscopy in the management of CP. Experts believe that endoscopic management has an important role in patients[24] as a primary therapeutic measure in poor surgical candidates where medical management fails. Recent evidence by Díte *et al*[25] suggests that surgical outcomes were more durable than endoscopic therapy in patients with a dilated pancreatic duct (PD), stones and/or strictures[25]. Cahen *et al*[26] recently reported better outcomes in pain control after surgery than with endoscopic intervention. Although these studies indicate surgery might be a better intervention than endoscopy, it needs to be pointed out that neither one of those studies came from centers using routinely ESWL, which is now incorporated into the management of patients with pancreatic stones[27]. Finally, endoscopy remains a highly effective intervention in patients with severe comorbidities and can also serve as a bridge to surgery[28].

PANCREATIC STRICTURES

Pancreatic strictures can be caused by prior stones, recurrent inflammation or fibrosis[29]. In cases of pancreatic stricture, where malignancy is suspected it is crucial to obtain cross sectional imaging followed by endoscopic ultrasound with fine needle aspiration (EUS-FNA) of any pancreatic masses. In the absence of a definitive mass, pancreatic brushing should be performed, keeping in mind that the threshold for referral to surgery in those cases should be low[30-32].

The management of benign strictures includes dilation and stenting (Figure 1). The number of strictures, the location of the strictures and the length of the stricture play key roles in determining the efficacy of endotherapy.

Symptomatic patients with a single stricture in the main PD in the head of the pancreas are the best candidates for ERCP with stenting[33]. It is generally accepted that patients with multiple strictures along the main PD, the so-called "chain of lakes" appearance, are not good candidates for endotherapy[33].

Table 1 summarizes the results of endotherapy in ref-

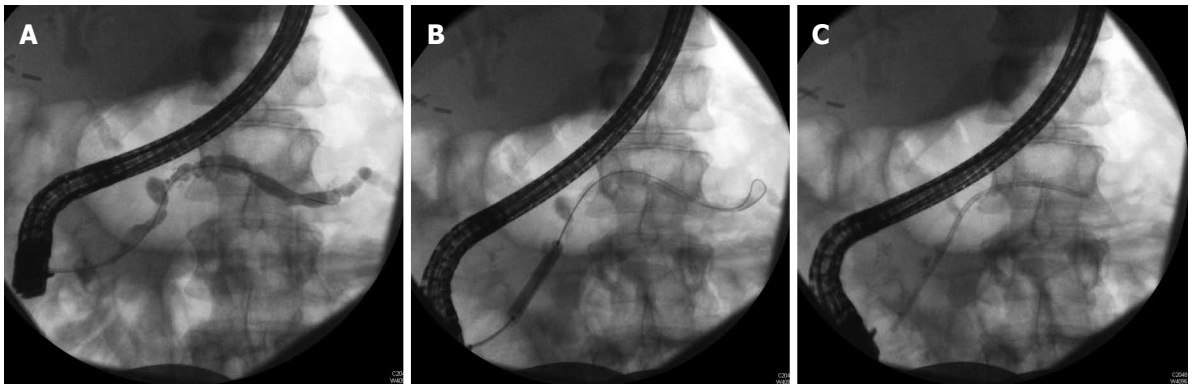

Figure 1 Management of benign strictures includes dilation and stenting. A: Distal pancreatic stricture in a patient with chronic pancreatitis; B: Dilation of the distal pancreatic stricture; C: Placement of a pancreatic stent (8.5 Fr x 12 cm).

Table 1 Summary of endotherapy in treatment of pancreatic strictures

Study	No. of patients	Tech success (%)	Average follow up time (mo)	Percent improvement in pain (%)
Weber *et al*[103]	19	89.4	24	89.4
Costamagna *et al*[40]	19	83.3	38	84
Eleftherladis *et al*[39]	100	70	69	70
Rosch *et al*[35]	1018	88	60	85
Eisendrath *et al*[104]	100	100	69	70
Layer *et al*[105]	66	NA	36	50
Cremer *et al*[106]	75	NR	37	94

NR: Not reported; NA: Not applicable.

erence to pancreatic strictures. Wilcox[34] summarized the available studies on this topic. The 15 series analysis has a total of 1500 patients. Among the 1500 patients, benefit was seen in 31%-100% of patients with a wide follow-up time period from 8-72 mo. An important finding from these studies was that complete stricture resolution is not needed for the resolution of pain.

The technique of stenting the PD in the event of strictures involves dilation prior to stenting. Dilation can be performed by wire guided balloons (4-6 mm), bougie or with a Soehendra stent retriever. Polyethylene pancreatic stents are then deployed for main pancreatic duct MPD stricture as large as possible to mimic a "pancreatico-duodenostomy"[12,27,33,35,36].

Pain relief is seen in 70%-94% of patients after stent placement (Table 1). Ductal decompression is indicated if the main PD above the stricture is significantly dilated (large duct disease). The strategy remains that the stents are prophylactically exchanged every three months[37]. In some cases, the stent can get clogged, however it will continue to remain effective by what is known as the "wick" effect[38].

It is important to note, however, that after stent removal the rate of recurrence of a main PD stricture is high. In fact, Eleftherladis *et al*[39] reported the stricture relapse rate after a 2 year follow up period was as high as 38%, with these patients require repeat stenting.

Although the approach of multiple stents for PD strictures seems promising[40-42], to our knowledge, at the time of writing, there have been no studies comparing single and multiple stenting procedures for PD strictures caused by CP.

For patient in whom conventional ERCP is not feasible or fails, access and decompression of the main pancreatic duct using EUS-guided pancreatography has increased the success for PD drainage[30-32,43-45]. This constitutes a minimally invasive alternative to surgery in patient with altered anatomy or severe stone burden not responding to ESWL.

PANCREATIC STONES

Obstruction of the PD by calcified stones leads to increased pressure upstream from the stone causing increased intraductal hypertension. The data surrounding pancreatic stone removal is clear. Endoscopic therapy alone was found to be successful in 72% of patients with a 68% symptomatic improvement[35,46,47]. ESWL can relieve the elevated intraductal pressure by fragmentation of intraductal stone.

Upon fragmentation the stones can pass spontaneously[48,49], therefore ERCP is not obligatory unless there is an associated stricture. The primary limitation of ESWL is that it cannot be used to fragment larger stones. In such cases, laser lithotripsy might be more effective[50-53].

In 2007, Dumonceau *et al*[54] compared ESWL alone with ESWL in conjunction with endoscopic drainage of the main PD for pain relief. Two years after intervention, they noted a similar decrease in the number of pain episodes per year. As such, it was concluded that

Table 2 Studies that evaluated endoscopic shock wave lithotripsy with endoscopic retrograde cholangiopancreatography for chronic pancreatitis

Study	Total patients	No. of patients in any amount of pain at follow up	Duct clearance	Mean follow up time (mo)
Sauerbruch *et al*[107]	8	8	8	11
Den Toom *et al*[108]	8	8 (7 pain relief)	8	17
Sauerbruch *et al*[109]	24	24	24	24
Delhaye *et al*[60]	123	88	123	
Schneider *et al*[110]	50	39	48	20
Van der Hul *et al*[111]	17	17	17	30
Wolf *et al*[112]	12	9	12	19-22
Schreiber *et al*[113]	10	7	10	12
Johanns *et al*[114]	35	23	16	NA
Ohara *et al*[115]	32	7	24	44
Matthews *et al*[116]	19	13	19	6 mo-6 yr
Costamagna *et al*[117]1	35	32	35	6
Adamek *et al*[49]	80	80	NA	NA
Brand *et al*[55]	48	17	48	7
Karasawa *et al*[118]	24	12	24	12
Kozarek *et al*[36]	40	28	NA	2.4 yr
Rubenstein *et al*[119]	23	NA	23	NA

[1]Pain relief was not a primary end point. NA: Not applicable.

ESWL alone was a safe and effective modality of treatment in reducing pain in CP with stone only disease and addition of endoscopic measures added costs to patient care, with no significant reduction in pain relief[54]. Endotherapy in conjunction with ESWL has been shown to increase stone clearance rates and to improve long-term outcomes[36,49,55-60] in patients with stone and stricture disease. In one study Kozarek *et al*[36] were able to show that surgery was avoided in 80% of patients who underwent ESWL. with decrease in narcotic use and reduction in hospitalizations (Table 2).

PANCREATIC PSEUDOCYSTS

A total of 20%-40% of patients with CP can develop this complication[61]. Intraductal hypertension within the main PD, or the rupture of a branching duct can lead to formation of pseudocysts. Pseudocysts[62] who fail to resolve spontaneously and are symptomatic require drainage. Drainage is indicated if there is pain, infection or evidence of obstruction[61,63,64].

The modality employed for drainage is also important. There are two major routes of endoscopic drainage-transmural and transpapillary. The route chosen depends on the size, possible communication between the pseudocyst and the pancreatic duct. There appears to be a trend in the literature for transmural drainage versus transpapillary[65] with an attempt to seal any possible leak or draining a proximal duct by crossing a stricture[65]. Several studies place the technical success of transmural drainage of pseudocyst at 85%-100%. The recurrence rate range from 10%-15% with complications between 10%-34%[63,66-68].

In recent years, EUS-guided pseudocyst (EGPD) drainage has gained in popularity since it allow to avoid intervening vessels and target more challenging collections safely when compared to conventional transmural drainage techniques (CTDT)[69-71]. Our team[64] and others[72] have demonstrated that EUS-guided drainage and conventional transmural drainage techniques have fairly comparable rates of success and similar rates of complications if non bulging collection and patient at higher risk of bleeding are selectively drained using EGPD.

ENDOTHERAPY ON BILIARY DUCT STRICTURES

Benign strictures can also form within the biliary ductal system in CP, and if left untreated can lead to jaundice, cholangitis and biliary cirrhosis[41,73]. Traditionally benign biliary strictures in CP are treated by surgery, but as with all surgeries the procedure is invasive and can involve significant morbidity especially if patients have other accompanying co-morbidities such as CP and/or liver disease. Morbidity and mortality of surgical treatment of post-operative biliary strictures is low, with mortality rates ranging from 0%-2.2%, whereas post-operative morbidity rates approaching almost 43% in some studies[74-76]. The multiple stent placement technique was initially popularized by Costamagna *et al*[40] for the treatment of postoperative strictures. In their study, stricture resolution was observed in 95% of patients at stent removal, and at follow up (average time of 38 mo after stent removal) 84% of patients were pain free and only 10.5% (2 patients) had recurrence of stricture.

They reported good long term results in treatment of post-operative biliary strictures by insertion of plastic stents after greater than a ten year follow up. While, success is dependant on the number of sessions and the number of stents placed, it appears that this maybe a reasonable first-line option[42]. Several groups have studied biliary strictures and endoscopic approach to treatment, and in all cases average stricture resolution was reported between 10%-33% (Table 3)[57,77-83].

Table 3 Summary of studies that evaluated efficacy of endoscopic biliary polyethylene stents for treatment of common bile duct strictures

Study	Total patients	Success rate (%)-short term	Stricture resolution (%)	Stent occlusion (%)	Stent migration (%)	Follow up time (mo)
Deviere *et al*[85]	25	100	3 (12)	32	40	14
Barthet *et al*[83]	19	100	2 (11)	0	5	18
Smits *et al*[82]	58	100	16 (28)	62	7	49
Kiehne *et al*[81]	14	100	2 (16)	36	NA	NA
Vitale *et al*[80]	25	100	20 (80)	12	8	32
Farnbacher *et al*[79]	31	100	10 (32)	29	23	24
Eickhoff *et al*[78]	39	100	12 (31)	33	10	58
Average	30	100	30	29.14	17.16	32.5

NA: Not applicable.

Uncovered metal stents have also been evaluated. Since biliary strictures related to CP can be difficult to treat with plastic stents, there have been several studies that examined the use of uncovered self-expanding metal stents (USEMS) in patients with primarily CP[84-87]. Deviere *et al*[85] deployed USEMS in patients (n = 20) with CP, and initially demonstrated relief of cholestasis for up to 33 mo for 18 patients. Repeat ERCP 3 mo later demonstrated that the stent was embedded within the bile duct wall. All subsequent studies confirmed that uncovered metal stents proved to be problematic due to epithelial hyperplasia, occlusion, and the inability to easily remove the stent without overwhelming evidence of improved patency or stricture resolution[88]. This lack of removability also predisposes the patient to chronic inflammation and a potential for cholangiocarcinoma.

Covered metal stent, partially or fully covered have been used, with stricture resolution for partially covered metal stent[89] noted to be about 77% in CP, whereas fully covered metal stents provided a success rate of 83%[90]. Given the limitations noted with uncovered stents, and in an effort to improve patency, partially covered self-expanding metal stents (PCMS) were assessed in this biliary stricture related to CP. They were noted to be easier to remove, offering the option of temporary placement[91-93]. Cantù *et al*[94] placed PCMS in patients with CP and associated common duct stricture who failed prior plastic stent therapy. All the patients responded initially but with a median follow up of 22 mo (range 12-33 mo), 7 patients developed stent dysfunction, requiring re-intervention. Stent patency, however, decreased over time, from 100% at 12 mo to 37.5% at 36 mo and none of the PCMS were removed during the study period, demonstrating that PCMS left in place over time decrease in patency, requiring additional endoscopic interventions[94]. Another similar study deployed PCMS in 6 patients with limited patency (2/6) at 35 mo (range 33-37 mo) follow up. In addition, this study compared uncovered (n = 18) to PCMS and found longer patency with uncovered stents (mean 46 mo *vs* 20 mo, P = 0.002), although overall follow up was much longer for uncovered stents (mean 61 mo), which could account for the significant difference[86].

Kahaleh *et al*[95] performed the largest series of patients (n = 79) with partially covered metal stents coated with Permalume (Wallstent, Boston Scientific, Natick, MA). Sixty five patients had stent left in place for a median of 4 mo (range 1-28 mo) and removed once successful treatment was confirmed. Follow up after stent removal was a median of 12 mo (range 3-26 mo). Three patients developed a stricture at uncovered proximal portion, 3 failed primary therapy and 2 developed duodenal edema preventing SEMS insertion, resulting in 90% success (59/65). Successful resolution of the stricture was noted to be lowest with strictures related to CP (17/22, 77%)[95]. As a follow up to this study, Sauer *et al*[96] further analyzed long term response of those patients. Notably, migration occurred with 15 stents, as well as intimal hyperplasia and stent embedment into the mucosa in 7 patients each respectively[96].

Fully-covered self-expandable metal stents

With limitations related to partially covered metal stents namely epithelial hyperplasia at the uncovered portions and migration, fully covered metal stents (FCSEMS) were then tried in this indication (Figure 2). Cahen *et al*[97] published a series of 6 patients with strictures resulting from CP receiving FCSEMS (Hanaro; M.I.Tech Co., Ltd., Seoul, South Korea), with 66% resolution, however 2 stents were unable to be removed requiring plastic stents placement through the other metal stent. More recently, Mahajan *et al*[90] analyzed a FCSEMS with anchoring fins (Viabil, Conmed, Utica, NY) to treat benign biliary strictures. A total of 44 patients (28 men, median age 53.5 years) were included. Etiologies included 19 CP. Complications were observed in 6/44 (14%) patients after placement, and 4/44 (9%) patients after removal, mainly pain and post ERCP pancreatitis. Lower rate of resolution was seen with CP (58%) and moderate difficulty in deploying and removing the stent due to its anchoring fins proved to be limitations in its widespread use. The anchoring fins also caused ulceration and bleeding with stent extraction[90].

A follow up study came from the same group with 55 patients and subsequent mean stent time of 126 ± 74 d and follow up of 524.2 ± 297.7 d. The success rate was 67% for those with CP and 71% for other etiologies[96].

The data that we are seeing in literature on FCSEMS

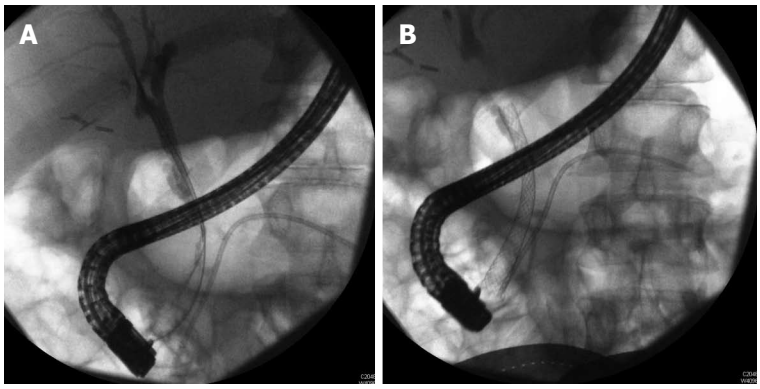

Figure 2 Fully-covered self-expandable metal stents. A: Distal biliary stricture in the setting of chronic pancreatitis; B: Placement of a fully covered metal stent (10 mm x 60 mm) draining the bile duct.

are promising, but larger randomized control trials are needed to evaluate this treatment modality. It is conclusive however, that endotherapy in treatment of biliary strictures is a good option for high risk surgical patients and for those who prefer a less invasive approach.

EUS-GUIDED CELIAC PLEXUS BLOCK

Celiac plexus block (CPB) is performed via a gastric approach using EUS-guidance and has high success rates and relatively low complication rates. EUS-guided CPB is preferred over CT-guided CPB not only because there are fewer side effects[98] but also because of clarity obtained via EUS. CPB can be performed by injection of anesthetics and/or steroids. Celiac plexus neurolysis, used for pain secondary to malignancy, is similar but involves injection of pure ethanol which results in complete destruction of the celiac plexus. EUS allows for live imaging of the celiac space which improves visualization. EUS guided celiac plexus block improves pain in about 50% of patients for a period of 3-6 mo[98]. In a prospective randomized study, Gress *et al*[98,99] compared EUS to CT-guided CPB for the treatment of CP pain and discovered that about 50% of patients in the EUS group had significant pain reduction. In addition, about 40% (8 wk group) and 30% (24 wk group) of the EUS-guided CPB had continued benefit. This, when compared to 12% (12 wk) in the CT-guided CPB, clearly suggest superiority of the EUS method.

Several retrospective and prospective studies have put the success rate was as high as 95%[98-101]. While technical success has been high, long term pain relief are disappointing. Short-term pain improvement was approximately 50%, whereas long term pain relief at 24 wk was only 10%. A similar number has been achieved for short-term pain relief by Kaufman *et al*[102].

Given the low long-term success rates, EUS-guided celiac block should be considered as a temporary measure. It should be considered in acute flares of chronic pain in those patients with limited options.

Surgical options

Advances in understanding the pathogenesis of CP combined with progress in technology have led to an emerging role of endoscopy in the management of CP. Experts believe that endoscopic management has an important role in patients[24] as a primary therapeutic measure in poor surgical candidates where medical management fails. Recent evidence by Díte *et al*[25] suggests that surgical outcomes were more durable than endoscopic therapy in patients with a dilated PD, stones and/or strictures. Cahen *et al*[26] recently reported better outcomes in pain control after surgery than with endoscopic intervention. Although these recent studies that indicate surgery as a better intervention than endoscopy, endoscopy is a highly effective intervention especially in patients who are high-risk surgical candidates especially if combined to ESWL. Delhaye *et al*[28], concluded that endotherapy can also serve as a bridge to surgery.

Díte *et al*[25] analyzed patients with CP secondary to large duct CP and compared endoscopic therapy to lateral pancreatojejunostomy procedure, and found that in the randomized and the non-randomized groups the results were similar. Moreover, on a five year follow up, patients in the surgery group were more likely to be pain free than in the endoscopic group. Cahen *et al*[26] also reported similar results. The primary difference between the two studies was that in the former study, endoscopic techniques were not optimized. Specifically, it did not involve patients undergoing cumulative stenting, or repeat treatment after recurrence, and it did not include ESWL.

CONCLUSION

CP is a disabling disease with serious complications affecting quality of life. There have been significant advances particularly on the endoscopic front with advent of endoscopic techniques such as pancreatic stenting, ESWL, pseudocyst drainage and EUS-guided access and therapy. A multidisciplinary team approach with judicious and appropriate utilization of the medical, endoscopic and surgical treatment options holds promise to revolutionize patient care. Given the variability in the presentation and patient preferences, treatment should be tailored on a case-to-case basis.

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BRIEF ARTICLE

Endoscopic knot tying: *In vitro* assessment in a porcine stomach model

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Abstract

AIM: To determine if surgical knotting performed *via* endoscopy is an effective closure method for natural orifice translumenal endoscopic surgery.

METHODS: The proposed method was tested on an *in vitro* pig stomach model using standard endoscopy suite materials. A single use laparoscopy trocar (Versaport Plus manufactured by Tyco Healthcare) was fixed onto a plastic rectangular box in a horizontal position. A fresh pig stomach was tightly attached *via* its esophageal end to the trocar opening on the inner side of the box. The stomach cavity was closed at the duodenal end with Kocher forceps. A standard upper gastrointestinal endoscope fitted at its tip with a transparent plastic cap was introduced into the stomach through the outer trocar opening, so that the passage of the surgical trocar would mimic the passage of an esophagus. The stomach was subsequently inflated, followed by irrigation and washing. A neutral electrode of an electrocautery unit was placed inside the plastic box, underneath the pig stomach. The stomach's outer surface was kept moist using normal saline in order to maintain the natural elasticity and to ensure good contact with the electrode.

RESULTS: The submucosal space on the anterior face of the stomach was accessed using the technique of endoscopic submucosal dissection. First, a site on the anterior face of the stomach was chosen, near the angle. Then, saline was injected into the submucosa with a standard endoscopic needle, so as to create a 20 mm diameter elevation. A linear 15 mm vertical incision was created at its center using a Dual Knife (KD650U manufactured by Olympus). This incision was used to access the submucosal space, and about 10 mm was dissected on both sides of the incision. The endoscope was then pushed through to the outside of the stomach after dilating a small puncture made by the Dual Knife in the *muscularis propria*, which simulated the peritoneoscopy procedure. Then, a 0.025" guidewire (Jagwire/450 cm manufactured by Boston Scientific) was inserted into the puncture, followed by a dilating balloon (Quantum TT manufactured by Cook Medical) that was used to enlarge the aperture orifice. After withdrawing the scope back into the stomach, the procedure continued with guidewires being passed from the submucosal space into the gastric lumen through small orifices on the left and right sides of the mucosal opening. These orifices were made with the Dual Knife, and the guidewires were inserted *via* a guiding catheter (HGC-6 manufactured by Cook Medical). As the guidewires were pulled outside of the stomach, they were replaced with a single surgical suture that had been initially attached to their tip and was now untied. Finally, one loop of this surgical suture was formed on the exterior. One loop end was fixed while the opposite suture end was pulled by biopsy forceps through the endoscope channel as the scope was inserted into the stomach. The loop was advanced until it approached and fixed the two mucosal incision margins. Three alternating loops were made in this manner to create a genuine tight surgical knot.

CONCLUSION: Endoscopic knotting of the gastric wall is feasible, but an *in vitro* survival study is necessary to validate clinical significance.

Key words: Endoscopy; Endoscopic submucosal dissection; Natural orifice translumenal endoscopic surgery; Suture; *in vitro*

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INTRODUCTION

The concept of natural orifice translumenal endoscopic surgery (NOTES) was introduced in 2004, when Kaloo *et al*[1] reported a successful transgastric peritoneoscopy performed in an *in vivo* porcine model. Since then, the variety of NOTES interventions using the porcine survival model has expanded to include splenectomy[2], gastrojejunostomy[3], hysterectomy[4], ligation of fallopian tubes[5], oophorectomy[6,7], cholecystectomy[8], appendectomy[9], hernia repair[10], pancreatectomy[11], and lymphadenectomy[12]. Human trials are currently under way[13].

From the beginning, two of the main scientific endoscopic societies have been involved in assessing and promoting research related to the NOTES procedures, namely the North American Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) group[14] and the European EURO-NOTES group[15]. In 2006, NOSCAR published a White Paper outlining twelve critical features that can impact the safety of NOTES to guide its appropriate usage and highlighted the need for increased research and analysis of data[16]. Gastric (intestinal) closure was designated as a very important area of research, and the group mandated a strict objective of the NOTES procedure to achieve closure with absolutely no leaks.

To date, the reported closure methods for the various NOTES interventions have used dedicated suture and anchor tools[17], such as T tags[18], purse string-modified T tags[19], Eagle Claw Ⅷ[20], flexible endoscopic stapler[21], purse string suturing device[22], and flexible Endostitch[17]. All of these devices are cumbersome and have not yet received approval for use in clinical settings.

Therefore, this study was designed to investigate the feasibility of performing a surgical suture of a stomach opening by using common endoscopy devices.

MATERIALS AND METHODS

A modified version of the *in vitro* porcine stomach model described by Hon *et al*[23] was used. Briefly, a trocar with radiolucent sleeve and 10-15 mm seal (Versaport Plus; Tyco Healthcare, Gosport, United Kingdom) was fixed onto a plastic rectangular box. A fresh pig stomach was tightly attached to the trocar on the inner side of the box *via* the esophageal opening. The duodenum was closed with a pair of Kocher forceps (Figure 1A). A standard gastroscope (GIF 160; Olympus, Rungis, France) fitted with a transparent straight plastic cap was inserted through the trocar (emulating passage through the esophagus) into the lumen of the stomach. The lumen was inflated and the procedure was performed as detailed in the Results.

RESULTS

The gastroscope-assisted knotting procedure was carried out with the following nine steps: (1) A 20 mm gastric submucosal bleb was created by injecting saline (25G 1-JectS; ABS Bolton Medical, Saint Michel/Meurthe, France) into the anterior inner face of the stomach, near the angle. A 15 mm linear incision was then made at the top of the submucosal elevation using a Dual Knife (KD650U; Olympus) coupled with a standard electrosurgical unit (Erbotom ICC200; ERBE, Tübingen, Germany); (2) The submucosal space was dissected at about 10 mm on both sides of the incision by introducing the cap-fitted endoscope inside the submucosal space (Figure 1B); (3) Peritoneoscopy was performed by the standard technique[1]. First, the Dual Knife was used to puncture the muscular layer from the submucosal space into the middle of the initial incision. A 0.025" guidewire (Jagwire/450 cm; Boston Scientific, Nanterre, France) was introduced into this orifice, followed by a 10 mm dilating balloon (Quantum TT; Cook Medical, Charenton le Pont, France) that was inflated to facilitate the scope's passage out of the stomach (Figure 1C). Finally, the balloon was deflated and the scope was retracted into the stomach; (4) On one incision side, a puncture was made in the mucosa from the submucosal space towards the lumen. A guiding catheter (HGC-6; Cook Medical) was introduced into this puncture to facilitate introduction of a 0.025" guidewire on the luminal side of the mucosa, traversing into the gastric lumen (Figure 2A); (5) After creating several loops in the stomach with the guidewire from Step (4), the endoscope was withdrawn, leaving the guidewire in place, and then reintroduced near it. The guidewire's distal end was captured with forceps (Radial Jaw; Boston Scientific) and pulled outside of the stomach (Figure 2B). Both ends of the guidewire were now outside the stomach, with the guidewire passing through an orifice from the submucosal space into the gastric lumen; (6) A 120 cm 4-0 surgical suture (Prolene; Ethicon, Issy les Moulineaux, France) was tied to one end of the guidewire. The other end of the guidewire was then pulled out, effectively dragging the surgical wire into the previously occupied position. The extracted guidewire was detached from the in-place surgical wire; (7) Steps (4), (5), and (6) were repeated on the second incision side, with minor modification. At step (6), the submucosal end of the guidewire was tied outside the stomach, with the submucosal end

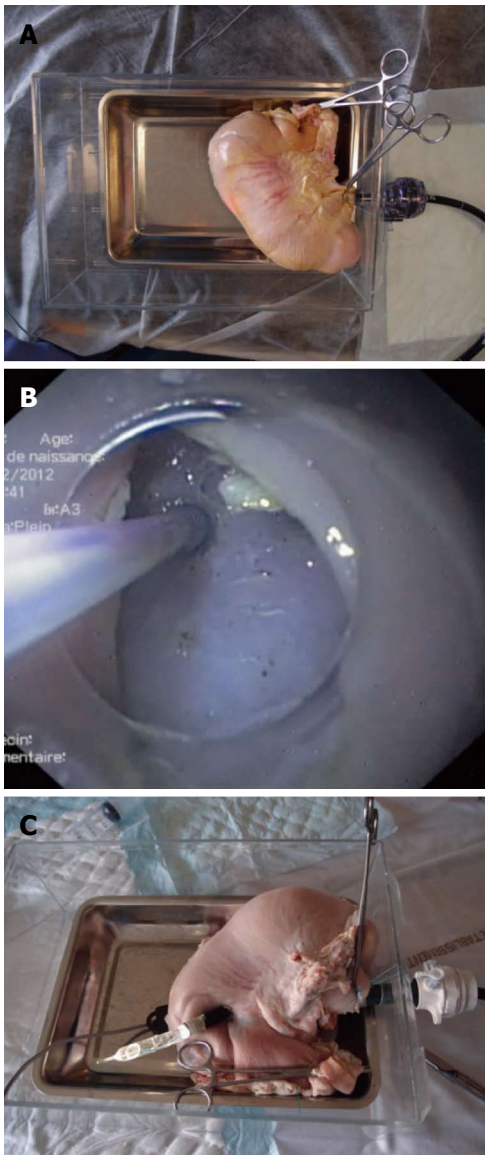

Figure 1 Endoscope. A: The "*in vitro*" pig stomach model with the endoscope in place; B: View over *muscularis propria* from the gastric lumen in the submucosal space created by endoscopic submucosal dissection. *Muscularis propria* is about to be punctured ("peritoneoscopy"); C: Endoscope outside of the stomach simulating peritoneoscopy, with the dilated balloon in the working channel.

of the surgical wire remaining in place on the first incision side. The guidewire was again pulled out, so that the surgical wire passed through both sides of the submucosal incision (Figure 2C); (8) A single loop had formed on the outside, and one wire end was fixed into place. Biopsy forceps were used to pull the other end through the working channel of the endoscope, simultaneously introducing the endoscope into the stomach and pushing the loop with the endoscope tip towards the incision line (Figure 2D). In this manner, the incision mucosal sides were brought towards one another as the loop was tightened. Three alternating loops were made to form the final surgical knot; and (9) The wire ends were cut with a reusable loop cutter (FS-5Q-1; Olympus) (Figure 2E). A photograph of the completed surgical knot is shown in Figure 2F.

DISCUSSION

The aim of this study was purely theoretical, by which we sought to prove that a surgical suture may be created using only commonplace endoscopy suite materials, without metallic clips, to close a hole in the wall of a hollow digestive organ. As such, the study has several important limitations.

Since the study was based on an *in vitro* model, neither the strength of the suture, its resistance nor tightness was evaluated. Moreover, other treatment-related quality parameters, such as infection rate and histological response, were not evaluated. Although infectious complications may be prevented in the *in vivo* model by antibiotic lavage of the stomach before gastric NOTES procedures[24]. Another limitation is that only a single knot was used to close a 15 mm incision, which would be insufficient for a surgical closure. We speculate that two or more suture wires may be passed through both incision sides and tightened at the end, so as to form two or more surgical knots and increase the fidelity of the closure. However, this may prove unfeasible since surgical wires could tangle or form spontaneous knots inside the stomach, beyond the operator's control.

Nonetheless, the endoscopic method does have an important safety advantage. The endoscopic surgical suturing reduces the risk of injury to organs adjacent to the stomach, which is a significant concern when using T-tags[25]. The method itself may also prove useful as a feasibility model for future development of safer suturing devices that work within a previously dissected submucosal space. In fact, some researchers have already attempted to investigate the utility and safety of an artificially generated submucosal tunnel, but the mucosal incision site had been closed with metallic clips[26]. Testing of this method in an *in vivo* animal model is necessary to better understand not only its clinical significance with NOTES interventions but also to help realize its potential for other applications.

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COMMENTS

Background

Traditionally, surgery has been the only method available for removing pathological tissue from the inner abdomen. Laparoscopic surgery and digestive endoscopy have made diagnostic and therapeutic procedures less invasive. Laparoscopic surgery requires creation of orifices in the abdominal wall to access the peritoneal space, while digestive endoscopy travels along and is confined to the digestive tract. In the last 10 years, however, the natural orifice translumenal endoscopic surgery (NOTES) approach passed the endoscope into the peritoneal cavity through a created orifice in the wall of the digestive tract.

Research frontiers

The NOTES approach has not yet been fully developed. Questions remain about how to prevent peritoneal infection, how to accurately stabilize the endoscope in the peritoneal cavity and obtain a good grip and orientation (triangula-

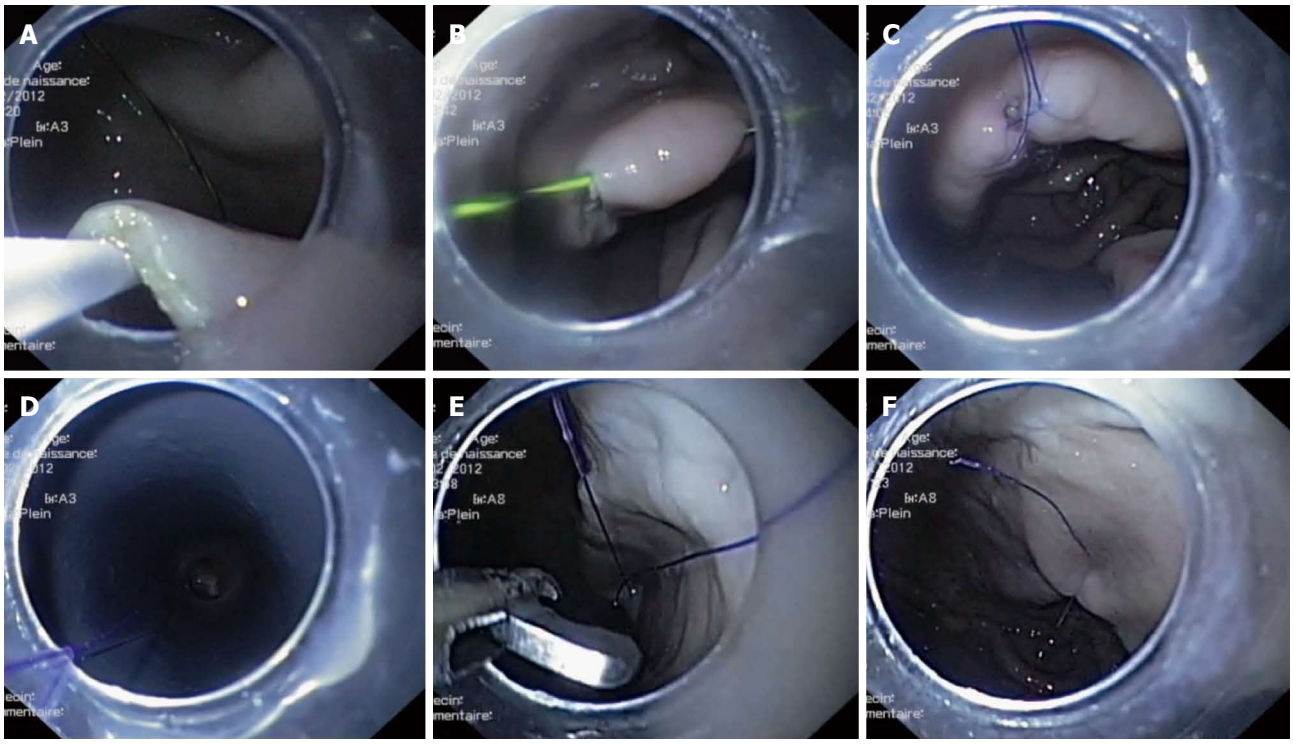

Figure 2 Natural orifice translumenal endoscopic surgery. A: Puncture of the mucosa from the submucosal space on the right side of the incision and passing a guidewire into the gastric lumen; B: The guidewire traverses the mucosa on the right side of the incision, both ends are outside; C: Surgical wire replaces the guidewire first on the right side, then is passed through both sides after replacing the guidewire on the left side; D: A loop formed outside is pushed with the endoscope (here at the rim of the transparent cap) at the mucosal incision so as to tighten the knot; E Cutting the wire ends; F: The final aspect of the surgical knot.

tion), and how to finally close the parietal access point. The simplest way to close the orifice is to use endoscopic metallic clips, which are already used for closing accidental perforations, for hemostasis, or for marking. More elaborate methods have been proposed, including endoscopic suture machines and staplers, or trans-parietal metallic tags tightened together. Yet, these methods are complicated, costly, high risk, and not approved for clinical practice.

Innovations and breakthroughs

The authors have described a method to close the digestive wall orifice with a surgical knot using only common endoscopy suite materials. This approach avoids the use of additional devices and reproduces the gold standard surgical closure method-the surgical knot.

Applications

The method may be used as a model for creating simple suturing devices that work within the submucosal space. It must first be validated by *in vivo* survival animal experiments.

Terminology

NOTES: Natural orifice translumenal endoscopic surgery, a method to perform abdominal surgery by entering the peritoneal space through small orifices made into hollow organs (i.e., stomach, colon, vagina, urinary bladder).

Peer review

The case is interesting and extremely rare. It is well written and is describing a new method of endoscopic suture. It can be accepted for publication an intra operative image during laparotomy would be of added value.

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CASE REPORT

Primary intestinal follicular lymphoma: How to identify follicular lymphoma by routine endoscopy

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Abstract

A 69-year-old Japanese female was diagnosed with primary intestinal follicular lymphoma. Esophagogastroduodenoscopy with high-definition imaging revealed not only the typical feature of whitish polyps of up to 2 mm in diameter in the duodenal second and third portions, but also more detailed morphology, such as enlarged whitish villi and tiny whitish depositions. These findings appeared to reflect the pathological structures; infiltration of lymphoma cells into the villi were probably seen as enlargement of the villi, and the formation of lymphoid follicles were shown as opaque white spots or tiny white depositions. Thus, the above features might contribute to the distinct diagnosis of intestinal follicular lymphoma. This case indicates that routine esophagogastroduodenoscopy can visualize microsurface structures, which can be pathognomonic and help to diagnose intestinal follicular lymphoma, even without magnifying endoscopy.

Key words: Follicular lymphoma; Gastrointestinal endoscope; Duodenal neoplasms; Gastrointestinal lymphoma; Microsurface structures

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INTRODUCTION

The number of patients newly diagnosed with primary intestinal follicular lymphoma is increasing as increasing numbers of endoscopists and gastroenterologists become familiar with this entity. The duodenum is the most frequently affected site, and the representative endoscopic feature, small whitish polypoid nodules up to 2 mm in diameter, is well known[1]. This feature has been described as "multiple polypoid lesions," "multiple small polyps," "multiple nodules" and "multiple granules"[2,3]. The ongoing development of magnifying endoscopy has provided more detailed endoscopic images of intestinal follicular lymphoma, enabling the identification of features such as enlarged villi, opaque whitish spots, and coiled vascular pattern within the villi[4-9].

We recently treated a patient with a typical case of primary duodenal follicular lymphoma. Her diagnosis was based on routine esophagogastroduodenoscopy findings without magnifying observations. The endoscopy findings were of a characteristic morphology, including enlarged whitish villi, tiny submucosal whitish depositions and multiple sites of involvement, in addition to the typical macroscopic features of whitish polypoid nodules. This case indicates that routine endoscopy can identify not only well known features such as whitish polyps or nodules, but also more detailed images that help to diagnose this disease, even without magnifying endoscopy.

CASE REPORT

A 69-year-old Japanese female presented to Onomichi Municipal Hospital in April 2012 with intermittent vague abdominal pain that had been present for the previous week. She had been taking betahistine mesilate for the prevention of Meniere's syndrome. The patient had no previous history of gastrointestinal or hematopoietic diseases. Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. All laboratory findings, including the levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R), were within the normal ranges.

Esophagogastroduodenoscopy was performed with a high-definition imaging system (CV-260SL, Olympus, Tokyo) and a videoendoscope (GIF-H260, Olympus). Esophagogastroduodenoscopy revealed whitish polyps around the ampulla of Vater (Figure 1A and B). Polyps were also noticed in the third portion of the duodenum (Figure 1C). A close-up view of the lesion in the second portion of the duodenum revealed that the lesion was composed of two components: enlarged whitish villi and tiny submucosal whitish depositions (Figure 2A and B). These structures were more clearly visualized with a narrow-band imaging view (Figure 2C). Based on these endoscopic features, duodenal follicular lymphoma was highly suspected. Biopsy samples contained lymphoid follicles in the duodenal mucosa, and these were comprised of small to medium-sized lymphoid cells which had also infiltrated into the villi (Figure 3). The lymphoid cells were positive for CD20, CD10, and BCL2, but negative for CD3. Small bowel involvement was evaluated by video capsule endoscopy, and whitish polyps were detected as multiple jejunal lesions (Figure 4). A colonoscopy revealed no abnormality.

A bone marrow aspirate and biopsy were performed, and revealed that there was no infiltration of lymphoma cells in the bone marrow. Computed tomography (CT) scans of the neck, chest, abdomen and pelvis detected neither lymphadenopathy nor a thickened gastrointestinal wall (including the duodenum). An 18F-fluorodeoxyglucose positron emission tomography scan showed no abnormal accumulations of 18F-fluorodeoxyglucose. Consequently, the patient was diagnosed with primary intestinal follicular lymphoma, which was localized to the duodenum and the jejunum. The clinical stage was considered to be stage I, based on the Lugano staging system for the classification of gastrointestinal tract lymphomas[10,11].

DISCUSSION

The use of high-definition imaging systems is well established in the field of gastrointestinal endoscopy, and such systems are now also widely used as a routine examination tool. High-definition imaging technologies provide high-resolution pictures to reveal more detail than the traditional video endoscopy systems. In the present patient, several key features, such as whitish enlarged villi and tiny whitish depositions under the mucosa, were visualized by high-definition imaging without a magnifying endoscopy system. To our knowledge, this is the first report to describe these microsurface structures as characteristic findings of intestinal follicular lymphoma being detected by routine esophagogastroduodenoscopy without magnifying observation.

Primary intestinal follicular lymphoma is a distinct variant of systemic follicular lymphoma that was established within the last decade[1,12]. The representative feature in the conventional endoscopic observation is well known as small whitish polypoid nodules that can be up to 2 mm in diameter[2,3]. More detailed microsurface structures have been reported by several authors, based on magnified endoscopic findings of intestinal follicular lymphoma[4-9]. Norimura *et al*[8] summarized the magnified endoscopic findings of six patients with intestinal follicular lymphoma, and they reported that abnormalities of the villi and the presence of opaque white spots are possible pathognomonic features of this disease. Our patient's endoscopic findings are in concordance with the report by Norimura. We speculate that these findings reflect pathological structures; infiltration of lymphoma cells into the villi are seen as enlargement of the villi, and lymphoid follicle formations are observed as opaque white spots or tiny white depositions. Thus, the above features might contribute to making the definite diagnosis of intestinal follicular lymphoma, although the sensitivity and specificity of these endoscopic features require further investigations.

In the present patient, esophagogastroduodenoscopy revealed multiple lesions, i.e., one lesion in the second portion and another lesion in the third portion of the duodenum. Video capsule endoscopy revealed additional lesions in the jejunum. Multiple sites of the gastrointestinal tract are frequently involved in patients with intestinal follicular lymphoma. Our previous study revealed that 46 out of 54 duodenal follicular lymphoma patients (85.2%) who underwent whole gastrointestinal tract surveillance had extensive involvement of the small

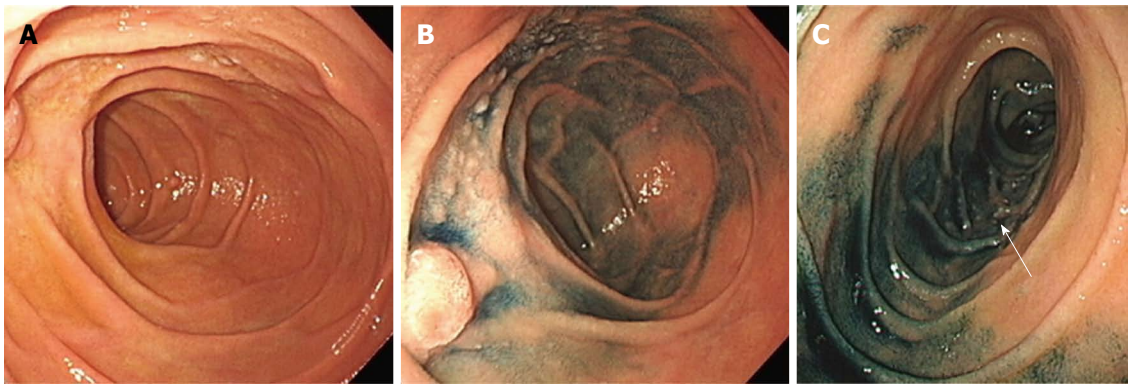

Figure 1 Images obtained during esophagogastroduodenoscopy. A: Mormal white-light observation revealed whitish polyps around the ampulla of Vater; B: Indigo carmine spraying increased the contrast of the lesion; C: Whitish polyps were also seen in the third portion (arrow).

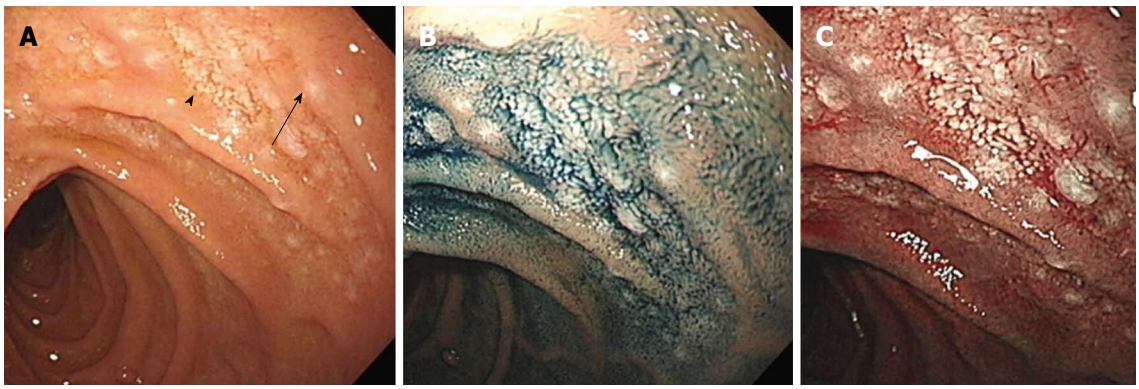

Figure 2 Close-up observation of the follicular lymphoma lesion. A: Enlarged whitish villi (arrowhead) and tiny submucosal whitish depositions (arrow); B: Indigo carmine spraying visualized these microsurface structures more clearly; C: Narrow-band imaging view also emphasized microsurface structures.

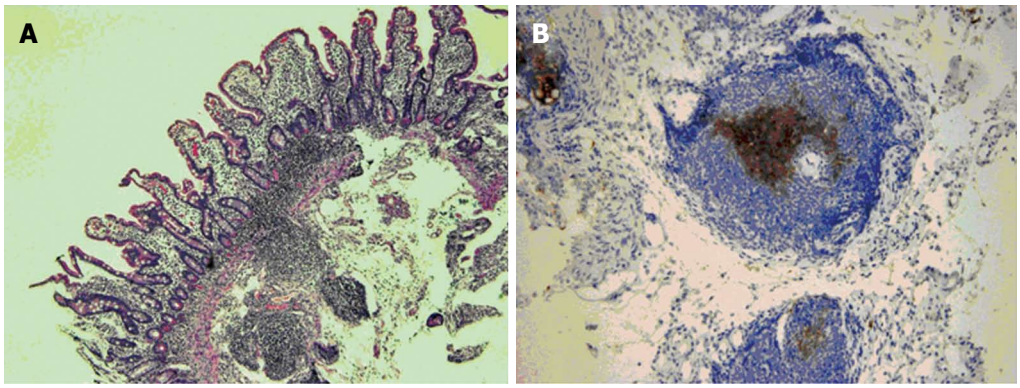

Figure 3 Pathological evaluation of the biopsy samples. A: Monotonous proliferation of small- to medium-sized lymphoid cells which formed lymphoid follicles and infiltrated into the villi; B: The lymphoma cells were positive for CD10 expression.

intestine[13]. Other researchers also reported that the percentage of patients with multiple lymphoma lesions in the small intestine ranged from 66.7% to 100%[5,14-17]. Consequently, multiple lesions in the duodenum are another feature that is suggestive of intestinal follicular lymphoma.

Pathologically, the major differential diagnoses of follicular lymphoma include mucosa-associated lymphoid tumors (MALT) lymphoma, mantle cell lymphoma and reactive lymphoid hyperplasia. Neoplastic cells in low-grade B-cell lymphomas, namely, follicular lymphoma, MALT lymphoma and mantle cell lymphoma, share morphological features to some extent. Such lymphomas are primarily composed of small- to medium-sized lymphoid cells of B cell origin. Generally, subcategorizing low-grade B-cell lymphomas requires immunohistochemical staining. Typical follicular lymphoma consists of CD10-positive neoplastic lymphoid cells. In mantle

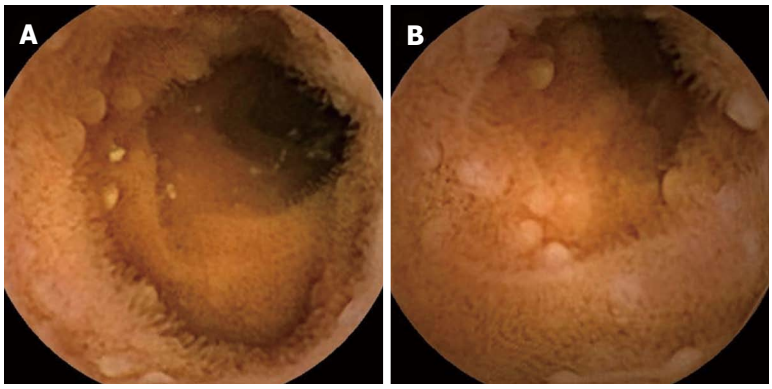

Figure 4 Multiple jejunal involvement revealed by video capsule endoscopy.

cell lymphoma, the lymphoma cells are positive for CD5 and cyclin D1. In contrast, the lymphoma cells in MALT lymphoma are negative for CD10, CD5 and cyclin D1. Therefore, biopsy and immunohistochemical examination should be performed to make the distinct diagnosis of follicular lymphoma, when endoscopists find the aforementioned endoscopic features of small whitish polyps, enlarged whitish villi, tiny submucosal whitish depositions and/or multiple sites of involvement in the intestine.

In conclusion, we present a case of primary intestinal follicular lymphoma. Enlarged whitish villi, tiny submucosal whitish depositions, and multiple sites of involvement, were demonstrated in addition to the typical macroscopic morphology of whitish polyps. Routine esophagogastroduodenoscopy by a high-definition imaging system can provide detailed features, helping to diagnose intestinal follicular lymphoma even without magnifying endoscopy.

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An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

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

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For articles of these sections, original articles and brief articles, 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/index.htm.

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Notes in tables and illustrations

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.

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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**. Hypertension, 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.

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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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