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THERAPEUTICS ADVANCES

Transumbilical laparoscopic-assisted appendectomy in children: Clinical and surgical outcomes

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Abstract

The aim of this paper is to present and describe transumbilical laparoscopic-assisted appendectomy in children, focusing on its technical aspects and clinical and surgical outcomes. The surgical charts of all patients aged between 0 and 14 years treated with transumbilical laparoscopic-assisted appendectomy admitted to the authors' institution from January 2009 to September 2013 with a diagnosis of suspected appendicitis following clinical, laboratory and ultrasound findings were reviewed. Operating time, intraoperative findings, need for conversion or for additional trocars, and surgical complications were reported. During the study period, 120 patients aged between 6 and 14 years (mean age: 9.9 years), 73 females (61%) and 47 males (39%), were treated with transumbilical laparoscopic-assisted appendectomy. There were 37 cases of hyperemic appendicitis (subserosal and retrocecal), 74 cases of phlegmonous appendicitis and 9 cases of perforated gangrenous appendicitis. It was not possible to establish a correlation between grade of appendicitis and mean operating time ($P > 0.05$). Eleven cases (9%) needed the use of one additional trocar, while 8 patients (6%) required conversion to the standard laparoscopic technique with the use of two additional trocars. No patient was converted to the open technique. Transumbilical laparoscopic-assisted appendectomy is a safe technique in children and it could be used by surgeons who want to approach other minimally invasive techniques.

Key words: Appendectomy; Children; Minimally invasive surgery; Transumbilical; Procedure

Core tip: Transumbilical video assisted appendectomy in children is safe and useful to approach minimally invasive techniques.

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INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen in the pediatric age. A clinical approach or laboratory tests resulting in a certain diagnosis for this condition are still to be found. The surgical techniques to perform appendectomy are manifold, ranging from the widely used open technique to more innovative minimally invasive approaches such as NOTES (Natural Orifice Transluminal Endoscopic Surgery)[1].

Transumbilical laparoscopic-assisted appendectomy [TULAA], used for the first time on children during the 1990s[2-4], profited from laparoscopy to implement a new minimally invasive approach.

In 1983, Semm described the standard three-port

technique for the first time; since then, the minimally invasive approach has gained wide acceptance among pediatric surgeons worldwide[2-5]. The transumbilical laparoscopic-assisted technique (TULAA) combines the advantages of both a good intra-abdominal laparoscopic visualization and the safety and quickness of extracorporeal traditional appendectomy. In 1991, Valla *et al*[6] reported the first significant case series treated using this technique, although they were all cases of uncomplicated appendicitis. Other authors, including Ohno *et al*[7], also reported a high number of cases (more than 400 patients) with excellent results, although again all patients had uncomplicated appendicitis.

The purpose of this study is to present the cases recently treated at the authors' institution for complicated and uncomplicated appendicitis with explanation of the technique used and its technical and pre/postoperative surgical aspects.

PREOPERATIVE MANAGEMENT

At the authors' institution, all patients reporting abdominal pain with suspected appendicitis without clinical or echographic signs of complicated appendicitis are managed conservatively for the first 12 h. They receive two doses of ampicillin plus sulbactam (50 mg/kg per dose) while their symptoms are monitored and blood tests are performed before opting for either conservative treatment or surgery. The minimally invasive approach currently in use at the authors' institution is transumbilical in all cases for the camera, standard laparoscopy or TULAA.

At least 30 min before surgery, the patient's umbilicus is carefully cleansed using a cotton swab impregnated with betadine. Patients do not receive prophylactic antibiotics since they have already received antibiotic treatment.

SURGICAL PROCEDURE

The patient is placed in the supine position under general anesthesia and mechanical ventilation. Once the patient is asleep, a vesical catheter is placed; the nasogastric tube is not positioned preoperatively but only during surgery if clinically indicated. The umbilicus is disinfected again and a wide sterile surgical area prepared: operation table sheets are placed at the level of the pubo-iliac line and below the rib cage (in order to have quick direct access to the abdominal cavity in case of complications, *i.e.*, massive blood loss). The operating surgeon stands on the left side of the patient, the assistant on the right and the scrub nurse next to the operating surgeon.

The laparoscopic video display is located on the right caudal side of the patient. The access to the abdominal cavity is achieved using a vertical incision directly through the umbilicus. A 10 mm trocar is then introduced and carbon dioxide (CO_2) pneumoperitoneum pressure is maintained at 10 mmHg with a flow of 1.5 L/min. It is paramount to maintain low values of insufflation and intra-abdominal pressure in order to reduce postoperative pain and to prevent cardio-circulatory complications. A zero-degree 10 mm operative telescope is inserted for abdominal examination (Figure 1A). The operation table is placed in the Trendelenburg position and then rotated to the left. From the operating canal of the telescope, a 5 mm traumatic grasper is introduced and the CO_2 pneumoperitoneum can be increased up to 12 mmHg; flow is also increased to 2 L/min to compensate for the gas leaks. The grasper is used to identify the appendix and to dissect retroperitoneal adhesions. When the tip of the appendix is freed, it is exteriorized through the umbilicus (Figure 1B). It is important to remember that the pneumoperitoneum needs to be deflated before extracting the appendix (to reduce the space between the cecum and the abdominal cavity and to maintain a moderate traction on the mesoappendix). At this point, a standard extracorporeal appendectomy is performed (Figure 1C). With subserosal, retrocecal or complicated appendicitis, it is possible to introduce one or two additional 3-5 mm trocars for graspers or a cautery hook. The use of more than one additional trocar converts the procedure into a standard laparoscopic appendectomy.

At the end of the procedure, the trocar is inserted again for final inspection (to avoid bleeding) and, if necessary, peritoneal toilet with suction is performed (*i.e.*, with phlegmonous appendicitis or perforated appendicitis). At the end of surgery, the surgeon determines whether it is necessary to use abdominal drainage, applied as in the standard open technique or using one of the trocar ports. The fascial defect is closed with absorbable sutures. The skin suture can also be performed with absorbable stitches (Figure 1D). Naropine 0.2% local anesthetic is usually used at the site of port insertion and a bulky pressure dressing is applied over the umbilical incision.

Postoperative analgesia is administered using ketoprofen or ibuprofen. Paracetamol can also be used.

POSTOPERATIVE MANAGEMENT

If there is no perforation, therapy with the same antibiotic is continued for 24 h and then stopped, while all cases of perforated appendicitis receive a regimen of ceftriaxone (100 mg/kg per day in one single administration) plus metronidazole (7.5 mg/kg per dose every 8 h) which is continued until the patient is afebrile for at least 48 h.

Re-feeding can start 12 h after surgery with uncomplicated appendicitis, 24 h in the other cases. Patients are finally discharged from hospital if they have been afebrile for at least 24 h, have no pain and have resumed full oral diet.

CASE SERIES

The surgical charts of all patients aged between 0 and 14 years treated with TULAA admitted to the authors' institution from January 2009 to September 2013 with a diagnosis of suspected appendicitis following clinical, laboratory and ultrasound (US) findings were reviewed.

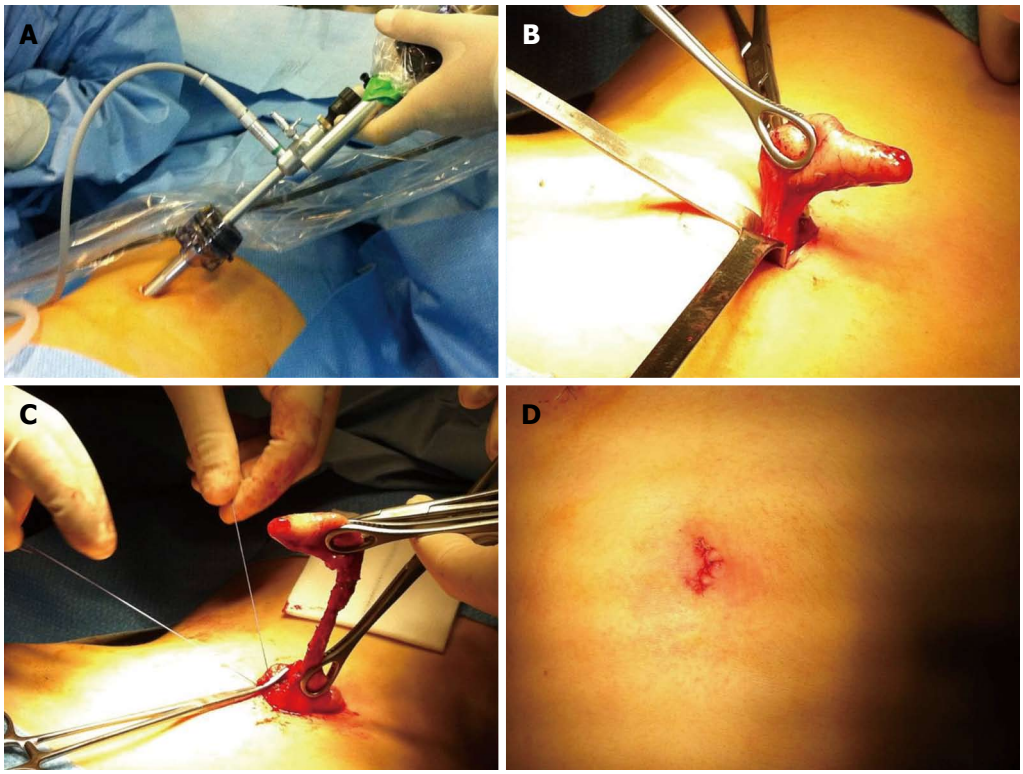

Figure 1 Surgical steps for video-assisted transumbilical appendectomy. A: Umbilical access for 10 mm port and operative camera; B: The appendix (phlegmonous) is externalized through the umbilicus; C: Open "classic" appendectomy; D: Skin closure: the umbilicus is closed with rapid 4/0 absorbable stitches.

Operating time, intraoperative findings, need for conversion or for additional trocars, and surgical complications were reported.

During the study period, 120 patients aged between 6 and 14 years (mean age: 9.9 years), 73 females (61%) and 47 males (39%), were treated with TULAA. There were 37 cases of hyperemic appendicitis (subserosal and retrocecal), 74 cases of phlegmonous appendicitis and 9 cases of perforated gangrenous appendicitis.

The grade of appendicitis was classified as reported in the literature[7]. Mean operating time was 58.6 min (range: 14-135 min), with differences depending on the grade of appendicitis: hyperemic = 55.5 min (range: 25-130 min); phlegmonous = 56.7 min (range: 14-120 min); gangrenous/perforated = 86.2 min (range: 55-135 min). It was not possible to establish a correlation between grade of appendicitis and mean operating time ($P > 0.05$). Eleven cases (9%) needed the use of one additional trocar, while 8 patients (6%) required conversion to the standard laparoscopic technique with the use of two additional trocars. No patient was converted to the open technique. Mean hospital stay was 3.7 d (range: 2-14 d). There were no cases of intraoperative complications, while postoperatively 5 patients showed umbilical infection (4%) and one patient had intra-peritoneal abscess which was managed conservatively with intravenous antibiotics.

DISCUSSION

If compared to the standard open technique, minimally invasive techniques have shown many advantages, such as easier exploration of the abdominal cavity, better diagnostic framework and differential diagnosis, as well as reduced postoperative pain. Hospital length of stay is also reduced: paralytic ileus resolves faster in patients who resume food intake early and therefore they are discharged more rapidly. In 1992, Pelosi first suggested the use of transumbilical laparoscopic-assisted appendectomy in adult patients, thus combining a laparoscopic procedure with the basic principles of the open technique and taking advantage from both the traditional and the laparoscopic approach[6-12].

TULAA was first described in pediatric patients in 1998 by C. Esposito and the first cases treated with this technique were reported by Valla *et al*[6] in 1991.

This video-assisted approach benefits from the laparoscopic technique since enlarged images allow the surgeon to observe the abdominal cavity and easily find the appendix. Also, the use of an operative optical trocar permits the introduction of graspers and cleansing instruments which are important in the most complicated cases of appendicitis. Finally, TULAA involves external appendectomy using the traditional open technique, thus reducing the length and costs of surgery.

Postoperatively, TULAA showed reduction of postoperative pain, shorter duration of pneumoperitoneum and diaphragm stimulation, and further improvement of the cosmetic result of wound scars[7,10-13].

From a technical point of view, TULAA is easier to perform than laparoscopy, with a consequently shorter learning curve for trainee surgeons. The authors' institution is a reference and excellence center for minimally

invasive surgery and their learning curve for laparoscopic appendectomy is of at least 15 surgeries, while for TULAA it is less than 10, regardless of grade of appendicitis. This is because TULAA involves a first laparoscopic approach followed by a traditional open technique for the appendectomy phase, resulting in being safe and efficient at the same time.

In the study series, 9% of cases (11 patients) required an additional port, while only 8 cases (9%) (three cases of gangrenous retrocecal appendicitis) required the placement of 2 additional trocars with conversion to the laparoscopic technique. The possibility of inserting an additional trocar in the most suitable position according to the intraoperative findings allows better management of this condition. Clearly, the learning curve with one trocar reduces surgery length as well as the need for additional trocars. In the authors' experience, higher complication rates and a more extensive use of an additional trocar occurred with this technique only during the first year of practice. It is also important to remember that TULAA is not an evolution of the laparoscopic technique; it is a different technique and surgeons with a wide laparoscopic experience also used additional trocars in the first cases treated with this technique.

There are many advantages in the use of TULAA: excellent diagnostic and therapeutic approach to the acute abdomen; observation of the entire abdominal cavity; high therapeutic reliability; high versatility; optimal cosmetic result; excellent postoperative recovery; and high feasibility, even in obese patients[13-16].

The current literature does not report real contraindications to the use of this technique apart from those generally indicated for pneumoperitoneum. As for laparoscopy, it is important to remember that insufflation pressure and flow rate must be kept as low as possible, especially in the pediatric age, in order to reduce postoperative pain. Specifically speaking for TULAA, it is necessary to deflate the abdomen before extracting the appendix since this prevents excessive traction on the mesoappendix and facilitates extraction of the appendix through the umbilicus.

CONCLUSION

According to the authors' experience, TULAA is a safe, minimally invasive approach in children suffering from acute appendicitis. It is also helpful as a training procedure for other minimally invasive approaches.

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MINIREVIEWS

Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management

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Abstract

Achalasia is an esophageal motility disorder characterized by failure of lower esophageal sphincter (LES) relaxation and is rare in children. The most common symptoms are vomiting, dysphagia, regurgitation, and weight loss. Definitive diagnosis is made with barium swallow study and esophageal manometry. In adults, endoscopic biopsy is recommended to exclude malignancy however; it is not as often indicated in children. Medical management often fails resulting in recurrent symptoms and the ultimate definitive treatment is surgical. Laparoscopic Heller myotomy with or without an anti-reflux procedure is the treatment of choice and has become standard of care for children with achalasia. Peroral endoscopic myotomy is a novel therapy utilized with increasing frequency for achalasia treatment in adults. More experience is needed to determine the safety, efficacy, and feasibility of peroral endoscopic myotomy in children.

Key words: Achalasia; Pediatrics; Surgical Heller myotomy; Balloon dilatation; Lower esophageal sphincter

Core tip: Achalasia is a neurodegenerative disorder of the lower esophageal sphincter which occurs less commonly in children compared to adults and patients present with progressive dysphagia, vomiting, and weight loss. Medical therapy including botulinum toxin injection and endoscopic dilatation have been associated with only transient relief of dysphagia symptoms as is also seen in adults. While current evidence also suggests that the surgical approach of laparoscopic Heller myotomy provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether peroral endoscopic myotomy is safe and equally effective in children.

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INTRODUCTION

Achalasia is a rare esophageal neurodegenerative disorder in the pediatric population. The disease is even more infrequent in children less than 5 years of age. The incidence of achalasia in childhood is 0.11/100000 children annually[1,2]. Overall, less than 5% of patients with symptoms present under the age of 15[3]. The disease is more prevalent in males and is most commonly idiopathic. Achalasia has been associated with Trisomy 21, congenital hypoventilation syndrome, glucocorticoid insufficiency, eosinophilic esophagitis, familial dysautonomia, Chagas' disease, and achalasia, alacrima, and ACTH insensitivity (AAA) syndrome[3].

Failure of the lower esophageal sphincter to relax

leads to the sequelae of achalasia. The pathophysiologic basis of achalasia is characterized by the degeneration of the inhibitory myenteric plexus that innervates the lower esophageal sphincter (LES) and esophageal body[4]. This leads to an imbalance in the inhibitory and excitatory neurons resulting in the failure of the LES to relax with swallowing, absence of peristalsis of the esophageal body, and increased LES resting pressures[5]. Goldblum *et al*[6] found a depletion or absence of myenteric ganglion cells, destruction of myenteric nerves, and chronic myenteric inflammation in 42 esophageal specimens. It is supposed that abnormalities in the parasympathetic innervation of the esophagus result in the esophageal dysmotility seen in achalasia; however the precise etiology of this abnormality is unclear[7].

Children usually present with progressive dysphagia, vomiting, and weight loss. Younger children and infants may also present atypically with recurrent pneumonia, nocturnal cough, aspiration, hoarseness, and feeding difficulties[3,8]. Achalasia in children is often misdiagnosed as gastroesophageal reflux disease (GERD). Children frequently present with failure to thrive, eating disorders, eosinophilic esophagitis, or asthma, which then leads to a delay in diagnosis for as long as 6-10 years[3]. Up to 50% of children are treated with antacids or prokinetics before the diagnosis of achalasia is identified[2].

DIAGNOSIS

Achalasia is diagnosed with a barium swallow study and may be confirmed with esophageal manometry. Barium swallow studies classically demonstrate a dilated esophagus with "bird's-beak" like tapering of the distal esophagus. Often, since there is a significant delay in diagnosis of achalasia in children, the esophagram study alone is diagnostic. Elevated resting LES pressure, absent or low-amplitude peristalsis, or non-relaxing LES upon swallowing are diagnostic findings on esophageal manometry in children with achalasia[1,2]. However, absence of these findings does not rule out the diagnosis of achalasia since LES function in children is heterogeneous. Partial relaxations are common and normal relaxations may also be present on manometry according to Morea *et al*[8]. Upper endoscopy and biopsy is reasonable to rule out esophagitis, Trypanosoma cruzi, malignancy, and other secondary causes of achalasia[1,4,5]. Our institutional protocol for work up consists of a barium swallow study, upper endoscopy, and endoscopic biopsy.

The various methods of treatment of achalasia involve reduction of LES pressure in order to facilitate esophageal emptying by: injection of botulinum toxin, oral administration of calcium channel blockers (Nifedipine), pneumatic dilatation, or esophageal myotomy (Heller) with or without an anti-reflux procedure.

MEDICAL THERAPY

Nifedipine, a calcium channel blocker, inhibits the trans membrane calcium influx in cardiac and smooth muscle and has been primarily used to treat achalasia in adults[5]. In children, the use of nifedipine has not been well studied. Maksimak *et al*[9] reported 4 children treated with nifedipine before meals who reported relief of symptoms likely related to a decrease in resting LES pressure. In either children or adults, nifedipine is not a definitive therapy and should only rarely be used as a bridge to relieve symptoms until pneumatic dilatation, Botox injection or myotomy can be performed[5,10].

ENDOSCOPIC THERAPY

Botulinum toxin injected into the LES acts on the excitatory terminal nerve endings of the myoneural junctions preventing acetylcholine release. Acetylcholine releasing neurons function in influencing the basal muscle tone[1]. Injection of botulinum toxin into the LES can be both diagnostic and therapeutic. Optimal dosing and injection frequency of botulinum toxin to relieve achalasia symptoms in children has not been well defined. After botulinum injection, the mean duration of symptom relief is 4 months, often requiring multiple treatments within a year[11]. In addition, botulinum toxin injection only provides permanent relief in 10%-40% of cases in adult patients[12] thus, will often require definitive surgical management.

PNEUMATIC DILATATION

Pneumatic dilatation or dilation of the functionally obstructed esophagus has been used in children. Recommended balloon sizes in children > 8 years is 35 mm[13,14]. Multiple dilatations are often required to achieve successful relief of symptoms although initial response predicts the success or failure of subsequent dilatations[15]. Hamza *et al*[14] reported a 90% success rate in children treated with multiple pneumatic dilations. The advantages of balloon dilatation include shorter length of stay, quicker recovery time, and decreased cost[13]. Pneumatic dilatation can be complicated by substernal pain, prolonged epigastric pain, esophageal perforation, aspiration pneumonia, and GERD[13,16-19]. Multiple studies suggest that in older children, pneumatic dilation is effective and safe initial treatment for achalasia and may spare children with achalasia an operation[13,14,20]. There are no long-term follow up studies in children to document success rates of pneumatic dilatation for achalasia. For adult patients, Eckardt *et al*[21] reported recurrence rates in as high as 60% in patients who underwent a single pneumatic dilation. Recurrent symptoms in children following multiple dilatations may require surgical myotomy[17,18,22].

SURGICAL

Despite multiple treatments for achalasia, surgery is the most definitive and successful treatment of choice. Laparoscopic Heller myotomy (LHM) involves making

Table 1 Patient demographics

	Mean	
Gender		
Female	13	54%
Male	11	46%
Age of diagnosis	11	5-18
Duration of symptoms	2.8 years	1-11 years
Presenting symptoms	*n*	Percentage
Dysphagia	20	83%
Emesis	14	58%
Weight loss	11	46%
Chest pain	10	42%
Regurgitation	4	17%
Odynophagia	2	8%

Table 2 Surgical approach

	Mean	
Age at surgery	12.9	5-8
OR time	124 min	45-213 min
LOS	2.7 d	1-6 d
Follow up	3.5 mo	1-12 mo
	n	Percentage
LHM	3	12.50%
LHM + TF	2	8.30%
LHM + DF	19	79.20%

LOS: Length of stay; LHM: Laparoscopic Heller myotomy; TF: Thal fundoplication; DF: Dor fundoplication.

a longitudinal incision in the muscle of the esophagus approximately 5 cm above the esophagogastric junction and extending 2-3 cm onto the cardia of the stomach. Laparoscopic Heller myotomy in children as in adults is the surgical treatment of choice[20,23-26].

Over the last 8 years at our institution, 24 patients were diagnosed with achalasia that subsequently underwent surgical treatment. Forty-six percent of the patients were male with a mean age of 11 (5-18 years). (Table 1) In this patient population, associated comorbidities included: mixed connective tissue disease scleroderma (1); Down's syndrome (1); inflammatory bowel disease (1); Sjogren's syndrome; and Pott's disease (1). The most common presenting symptoms were dysphagia (83%), emesis (58%), weight loss (46%), and chest pain (42%). Average weight loss was 9.9 kg requiring supplemental nutrition. Mean duration of symptoms prior to surgical treatment was 2.8 years, which was consistent with multiple studies[16,26-31]. Upper endoscopy in our patients commonly showed a dilated esophagus with retained food products. Approximately one-third of our patients had an abnormal biopsy. Four patients had acute esophagitis one of which was treated for Candida. Esophageal manometry was done in only 38% of our patients secondary to inability to tolerate the procedure. Only 2 patients (8%) who underwent myotomy were treated with nifedipine with only temporary relief of symptoms. Four underwent pneumatic dilatation (17%). In 1 patient, pneumatic dilatation was complicated by esophageal perforation requiring video-assisted thoracoscopic surgery (VATS) drainage and prolonged hospital stay. This patient subsequently underwent a laparoscopic Heller myotomy (LHM) and Dor fundoplication with resolution of symptoms of achalasia at 3 month follow up. Most of our patients (88%) underwent laparoscopic Heller myotomy with a Dor or Thal fundoplication. Average age at the time of surgical treatment was 12.9 years of age (5-18) (Table 2). Average operating time was 124 min.

In our series, we had only 2 intraoperative mucosal perforations, which were repaired primarily laparoscopically in children that had had LHM without fundoplication. Two children who had LHM with Thal fundoplication developed recurrent dysphagia requiring pneumatic dilations several months later. One patient who underwent a LHM and Dor fundoplication required a laparoscopic redo LHM and Dor for recurrent dysphagia. All of our patients receive a barium swallow study and a clear liquid diet on the first postoperative day. We have had no incidence of leak on the esophagram in our patients postoperatively or delayed perforations. We routinely discharge our patients on postoperative day 2 and our average length of stay is 2.6 d. Eight percent of our patients had recurrent symptoms of dysphagia postoperatively. One patient required revision of the initial operation 10 mo after the first operation (Table 3). There was a significant improvement in symptoms after the second procedure. As seen in other centers, most patients with recurrent dysphagia after surgical treatment for achalasia undergo balloon dilatation with improvement in their symptoms (Table 3).

The laparoscopic approach is superior to the open approach secondary to the well-recognized benefits including minimal pain, better cosmesis, shorter hospital stay, and faster return to normal activity for the child and parent/guardian[26]. Common causes of surgical failure are GERD and recurrent dysphagia. A partial fundoplication is commonly used to prevent GERD in patients following Heller myotomy. In a randomized controlled trial, Rebecchi *et al*[32] determined that laparoscopic Dor fundoplication after a LHM was superior to Nissen fundoplication because the recurrence rate of dysphagia was significantly higher in patients who received a Nissen fundoplication in their adult patients. There is some controversy as to whether an anti-reflux procedure should be performed in children at the time of LHM. Corda *et al*[24] concluded that an anti-reflux procedure is not required with a LHM for the prevention of GERD. Other studies have shown benefits and it is our practice to perform LHM and partial fundoplication[27,28,31,33].

The two primary complications of surgical management of achalasia are esophageal perforation and recurrent dysphagia. In our experience and review of

Table 3 Surgical management of pediatric achalasia

Ref.	*n*	Age (yr)	Symptom duration (mo)	Procedure	OR time (min)	Complications	Treatment	Length of stay (d)	Follow up (mo)
Pastor *et al*[16]	40	12.4	10.7	6 OHM 3 LHM 11 LHM + Nissen 21 dilation	186 156	1 perforation 2 perforations	Sutured Sutured	- -	75
Corda *et al*[24]	20	12 (5-15)	24	20 LHM	96 (60-160)	4 conversions OHM 5 dysphagia	 1 lap LOA 1 redo LHM 1 redo OHM	3 (1-5)	60
Esposito *et al*[26]	31	8.4 (5-15)	>12	31 LHM/Dor	120	3 perforations 5 dysphagia	2 sutured 1 redo HM 2 dilated 1 redo OHM	4 (3-8)	9-156
Tannuri *et al*[27]	15	12 (9-17)	30	15 LHM/Dor	90 (150-260)	2 dysphagia	1 botox injection	2.5 (1-4)	32.5 (2-96)
Patti *et al*[28]	13	15 (6-17)	24	13 LHM/Dor	144 ± 35	-	-	2	19
Lelli *et al*[29]	19	10 (1-17)	-	14 OHM 5 OHM + Belsey	-	2 dysphagia	2 dilation	8	108 (6-252)
Rothenberg *et al*[30]	9	12 (5-17)	6-24	4 THM 5 LHM/Dor	95 62	1 perforation 1 dysphagia 2 GERD 1 delayed perforation	Sutured Redo LHM Medical Rx Lap repair	2 1	-
Askegard-Giesmann *et al*[31]	26	15 (4-18)	-	1 LHM 2 LHM/Dor 23 LHM + Toupet	- 	1 perforation 1 perforation/aspiration 7 dysphagia 1 GERD	Sutured Sutured 3 redo LHM 3 dilation 1 botox Medical Rx	2.7 (1-4)	0-75 -20
Esposito *et al*[32]	8	6.3 (2-13)	> 121 LHM	6 LHM/Dor 2 LHM/Thal	120 (90-150)	3 perforations	3 sutured	4 (3-31)	6-60
Current Study	24	12.9 (5-18)	> 24	3 LHM 2 LHM/Thal 19 LHM/Dor	124 (45-213)	2 perforations 2 dysphagia	2 sutured 2 dilations 1 redo LHM	2.7 (1-6)	4 (4-24)

OHM: Open Heller myotomy; LHM: Laparoscopic Heller myotomy; THM: Thoracosopic Heller myotomy; Rx: Therapy.

the literature, there was 0%-26% recurrence rate of dysphagia after LHM with or without an anti-reflux procedure (Table 3)[16,24,26-30,33]. It is unclear if recurrent dysphagia is secondary to the nature of disease or failure of surgical treatment. Surgeon experience may contribute to decreasing rates of complications as suggested by Esposito *et al*[26] since their incidence of post-operative dysphagia dropped from 50%[33] to 16% with further experience. Our incidence of recurrent dysphagia is 8% compared to 11%, 16%, 25%, and 26%[29,25,26,31] in comparable sized series (19-31 patients). Perforation rates occur from 0%-15% (8% in ours) in larger series[16,24,29,31] but rarely require re-operation (Table 3). Accordingly, in smaller series and those from longer time periods in the past, perforation rates were higher (22%-50%) probably related to the establishment of a learning curve for the operation[30,33].

PER ORAL ENDOSCOPIC MYOTOMY

Peroral endoscopic myotomy (POEM) is a novel technique in the treatment of achalasia. POEM is one of few procedures utilizing natural orifice transluminal endoscopic surgery (NOTES) routinely in adults. POEM is an endoscopic procedure that directly treats the diseased tissue[23]. Pasricha *et al*[34] first described a submucosal endoscopic esophageal myotomy in animal studies for the treatment of achalasia. Inoue *et al*[35] coined the term peroral endoscopic myotomy and was the first to perform the procedure in 17 adult patients. Multiple studies have concluded that short-term outcomes of this procedure were safe[35-38].

Not all patients are suitable candidates for POEM. Contraindications include severe pulmonary disease, coagulation disorders, prior esophageal mucosal resection, or any prior therapy that has compromised the integrity of the esophageal mucosa[37]. POEM is performed utilizing flexible endoscopy, mucosal incision and dissection of a submucosal tunnel distally in the esophageal wall to approach the esophagogastric junction. A 2-3 cm longitudinal incision in the inner circular muscle approximately 4 cm from the LES, will produce similar results to

Heller myotomy[36,38]. A contrast esophagram is routinely obtained on the first postoperative day and the patient is started on a pureed diet if esophagram is normal[36-39].

Ren *et al*[40] reported 119 cases of achalasia treated with POEM, the most common postoperative complications included subcutaneous emphysema (55.5%), pneumothorax (25.2%), pneumomediastinum (29.4%), pleural effusion (48.7%), segmental atelectasis (49.6%), pleural effusion (48.7%), and pneumoperitoneum (39.5%). In this study, 13 patients with pneumothorax were treated with thoracic drainage and 2 patients with pleural effusion were treated with thoracentesis. The high incidence of pneumothorax, pneumomediastinum, subcutaneous emphysema, and pneumoperitoneum was attributed to the use of air insufflation during the procedure and subsequently this group now utilizes CO_2 insufflation[23]. Swanström *et al*[36] reported pneumoperitoneum in 3 out of 5 patients that were treated with Veress needle. Inoue and associates reported pneumomediastinum in multiple patients, however these patients did not require treatment although another patient in that series underwent thoracostomy drainage tube placement[39]. Feasibility of POEM is highly dependent on surgeon' s experience, duration of symptoms, prior pneumatic dilatations, and endoscopic therapies[41]. Nonetheless, multiple studies have reported POEM provides favorable outcomes and is relatively safe for the treatment of achalasia in adults[35-37,39-43]. Long-term outcomes (> 6 mo) for POEM in adult patients have been reported by Swanström *et al*[44] as significant in relieving dysphagia in 83%. Maselli *et al*[45] reported the first case of POEM performed in a 3-year-old with achalasia complicated by failure to thrive. At 1-year follow up, the patient was asymptomatic and had an appropriate weight for her age[45]. Familiari *et al*[46] reported 3 children treated with POEM for achalasia. There were no postoperative complications. In this study, 2 out of 3 patients had complete resolution of symptoms and the third patient had improvement in symptoms after 1-year follow up[46]. Although POEM is effective, minimally invasive, and safe in adults, there is also more recent evidence to suggest that the surgical approach (laparoscopic Heller myotomy) is more definitive and long lasting in relieving symptoms in these patients compared to endoscopic dilatation or botulinum toxin injection techniques[47]. It is apparent that effective therapy for children with achalasia is needed. Marlais *et al*[48] reported that children with achalasia have a significantly lower quality of life (QOL) compared to both children with inflammatory bowel disease and healthy children. While current evidence also suggests that the surgical approach provides lasting benefits for children with achalasia, future prospective evaluation will need to be conducted to ascertain whether POEM is safe and equally effective in children. For now, it is unclear; however pediatric surgeons are interested in learning this novel technique and employing its use in the management of pediatric achalasia.

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MINIREVIEWS

ESD training: A challenging path to excellence

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Abstract

Endoscopic submucosal dissection (ESD) has important advantages over endoscopic mucosal resection (EMR) for early gastrointestinal neoplasia treatment, but its difficult learning curve and associated risks have constrained its wider expansion. ESD training includes a comprehensive study of ESD basics, attending live cases and performing initial interventions in animal models, ideally under expert supervision. Mentoring methods in Japan and other Asian countries are reviewed, with a special concern in the conditions recommended for trainees to engage in an ESD program and achieve competence. Animal training is usually based on the well-known porcine model. *Ex vivo* models for esophageal, gastric and rectal ESD are cheap and easy to set up, whereas *in vivo* training requires special settings and veterinarian support. Nevertheless, it is advisable to gain experience in the live pig, with conditions that are similar to humans, before moving on to real patients. Particular attention is focused on colorectal ESD (CR-ESD), one of the most difficult locations for this technique. Since most of the potential lesions for ESD in Western countries are located in the colon or rectum, excellence in training is of paramount importance for successful outcomes in CR-ESD in the West.

Key words: Endoscopic submucosal dissection; Training; Early neoplasia; Animal model; Colorectal

Core tip: This mini review focuses on endoscopic submucosal dissection (ESD) training. ESD is a relatively novel advanced technique used for *en bloc* resection of gastrointestinal early neoplasia. ESD training has become a challenge for Western endoscopists due to several factors: low detection rate of early gastric cancer, the perfect scenario for starters; lack of experts in the technique for adequate tutoring; and finally, most of the target lesions in Western countries are colorectal neoplasias, representing the highest peak of difficulty in ESD. We will review some of the most important steps that could shape a training program in ESD, including animal training. Particular attention is focused on colorectal ESD.

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INTRODUCTION

The oncology field is already an important area of development for gastroenterologists[1] since diagnosis and/or treatment of early gastrointestinal neoplastic lesions is crucial for prevention and cure. Management of lesions with a low risk of lymph node metastasis usually comprises classic polypectomy and endoscopic submucosal resection (EMR). EMR has demonstrated good results dealing with esophageal, gastric, duodenal and colorectal lesions[2-5]. Ideal targets include flat lesions (Paris Classification 0-Ⅱa and 0-Ⅱb) less than 2 cm, although piecemeal resection is also possible with acceptable outcomes[2,6]. Endoscopic submucosal dissection (ESD) is a late step forward in therapeutic endoscopy for early gastrointestinal neoplasia[7] and has become a standard of care, not only in Japan where it originated in the late 1990s, but also in some

other countries and regions[8-17]. ESD has also spread in its indications: gastric, esophageal, colorectal, duodenal and even hypopharyngeal early neoplasia are potential targets, with excellent results[18]. New and exciting areas of research for ESD are now being explored, like the treatment of submucosal tumors[19,20] (Figure 1).

The main advantages of ESD compared to EMR are a higher *en bloc* and R0 resection rate[21-23], with decreased local recurrence, no limitation due to size of the lesion in certain circumstances and superior pathological assessment of the cancer invasion in the specimen[24,25]. Nevertheless, ESD is associated with a higher risk of severe complications (bleeding and perforation) (Figure 2), in addition to a particularly difficult and long learning curve[21,26-28]. The latter, together with the lack of experts available for tutoring, are the most important restricting factors for a wider expansion of ESD in Western countries[11]. The lower gastric cancer incidence, with a lower proportion of early gastric cancer diagnosed during upper endoscopy procedures, also contributes to the low penetration of ESD in Western areas[13,29]. Those are the ideal cases for initial training in human ESD, as recommended by experts[9,18,30]. Unfortunately, this painful scenario for training is aggravated by the fact that many potential lesions for Western endoscopists to perform ESD are mostly found in the colon and rectum, a particularly challenging location, even for Japanese experts[31,32]. Some of the most important aspects of ESD training, with a particular section focused on colorectal ESD (CR-ESD), will be reviewed.

JAPANESE EXPOSURE: THE ORIGINAL SOURCE

ESD was initially developed in Japan and Japanese experts have propelled this technique to its highest standards and excellent outcomes[33,34]. In Japan, the usual way of teaching new apprentices in ESD has traditionally consisted of supervised ESD procedures by senior endoscopists in referral centers (Figure 3). This scheme seems to have worked well in recent years, but as the number of physicians performing ESD and its indications are rising, it seems that even in Japan some kind of standardized ESD training program for teaching centers is needed[35]. Most of the candidates should have demonstrated advanced skills in therapeutic upper and lower endoscopy, as well as extensive knowledge of early neoplasia endoscopic assessment. Moreover, many mentors do consider aptitudes like perseverance, competence in dealing with stressful situations and awareness of own limitations on their mentee selection process.

Gastric ESD is contemplated as the first step in the ESD career since the easier position and thick wall facilitates the ESD approach with a lower risk of perforation. Screening programs in gastric cancer have boosted the detection and knowledge of early gastric cancer in Japan[36]. Basic competence in terms of *en bloc* resection and complication rate can be reached after 30 human gastric

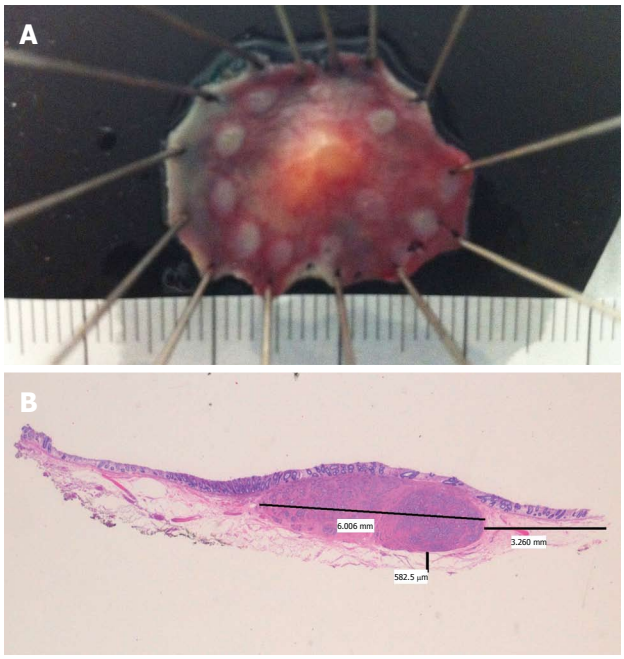

Figure 1 Rectal neuroendocrine tumor. A: Specimen fixed after successful endoscopic submucosal dissection; B: Hematoxylin and eosin × 10. Neuroendocrine tumor, 6 mm largest diameter. Free lateral and depth margins (R0) (courtesy of Dr. Isabel Salas, Puerta de Hierro University Hospital).

cases have been completed under expert supervision[28,37]. Tsuji *et al* have described excellent results for trainees who completed 27-30 gastric ESD after having attended 40 cases and later completing 20 cases of post-ESD preventive coagulation[38]. A recent study suggests that expertise similar to well-experienced endoscopists could be achieved after having completed 80 cases, including lesions within extended criteria (ulceration, large size *etc.*)[39]. Some suggested the criteria for skill advances monitoring as speed, size and *en bloc* resection rate[28], but the location in the stomach is also a decisive factor, with more difficult cases in the body and fundus[10,39].

For many foreign physicians with an interest in ESD, Japanese teaching centers are a good opportunity for first-hand exposure in its "natural" environment[40]. They can experience how the experts perform high quality diagnostic evaluation of target lesions and perform ESD. Essential knowledge to acquire includes, but is not limited to, dye and digital chromoendoscopy, magnification endoscopy, marking and initial approach to lesions, step by step ESD procedure, tools and devices, management of minor and major complications, post-ESD surveillance and specimen fixation and pathological assessment. Overseas endoscopists are not usually allowed to do hands-on training in humans in Japan, yet they can still practice ESD in animal models with the unique opportunity of onsite expert supervision[41] (Figure 4). Furthermore, it is possible to invite Japanese experts to Western centers to get tutoring support for an initial ESD approach[42,43] (Figure 5).

In recent years, relevant progress in ESD has been observed in other neighboring countries in southeast

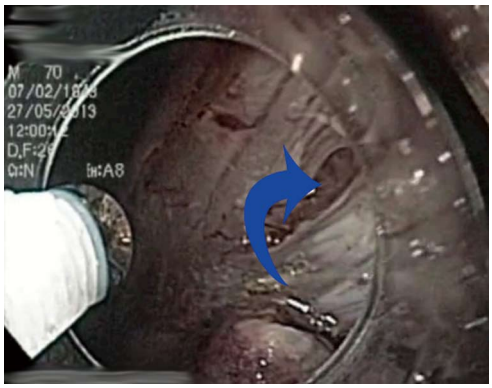

Figure 2 Small perforation (blue arrow) in the anterior wall of the stomach after endoscopic submucosal dissection of intramucosal adenocarcinoma (T1a, R0).

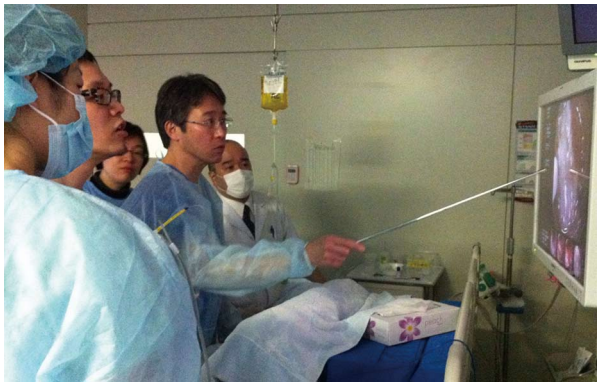

Figure 3 Professor Toyonaga supervising human endoscopic submucosal dissection case performed by young trainee. Kobe University Hospital, Japan.

Figure 4 Dr. Morita supervising live animal endoscopic submucosal dissection case performed by trainee (Dr. Herreros de Tejada). 2nd KOBE International endoscopic submucosal dissection and EUS-FNA Hands-on-Seminar Kobe University Hospital, Japan.

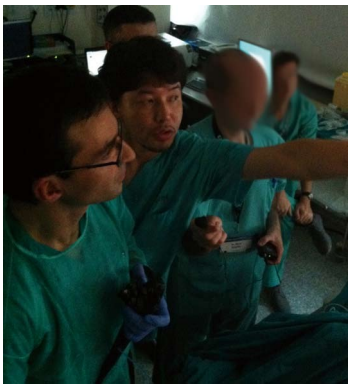

Figure 5 Dr. Morita supervising human rectal endoscopic submucosal dissection case performed by trainee (Dr. Herreros de Tejada). International endoscopic submucosal dissection Live Madrid 2013 Clinical and Hands-on Course. Puerta de Hierro University Hospital, Madrid, Spain.

Asia, mainly in South Korea[10,44] and China[45]. In South Korea, eligible trainees with a 2-year experience in endoscopy must observe 30-40 ESD cases to follow all steps of the procedure, including fixation of the specimen once completed; afterwards, they would serve as an assistant with knives to an expert endoscopist for 15-20 cases before being allowed to start ESD with small lesions in the antrum under close supervision[46]. As an additional reinforcement, the national Korean ESD group conducts an *ex vivo* hands-on course for trainees[30,47]. In the near future, we can expect high quality expert groups in Korea also offering additional opportunities for ESD training to overseas trainees.

ANIMAL TRAINING: THE WILD EXPERIENCE

Training in animal models is probably the best way to overcome some of the limitations in learning ESD[41,48]. Such a difficult technique must not be attempted in humans unless supervised by certified experts, or after an intensive animal training program has been completed and satisfactory outcomes have been achieved. The porcine model is similar to human anatomy, not expensive and widely accessible[46]. Reports of ESD in other species are scarce[16,49], including a description of a human excised portion from a sleeve gastrectomy[50]. Most studies have demonstrated the usefulness of the porcine *ex vivo* and *in vivo* for initial competence achievement in ESD, where regular endoscopes can be used and anatomic similarities in esophagus and stomach facilitates the approach[43,45,48,51,52]. The trainee can experience the early steps of the ESD process (marking, circumferential cutting and submucosal dissection), together with management of complications such as perforation and bleeding (only *in vivo* model). Some suggested the criteria for skill advances monitoring are speed and *en bloc* resection rate[53,54]. An animal training program in ESD requires appropriate settings and dedicated endoscopy equipment and materials (Figure 6), all of which is not commonly accessible to many trainees in their institutions. Some endoscopists attend special courses in ESD to get access to animal training, with good results in terms of skill improvement[43,45].

Ex vivo model

Harvested porcine organs like esophagus and stomach

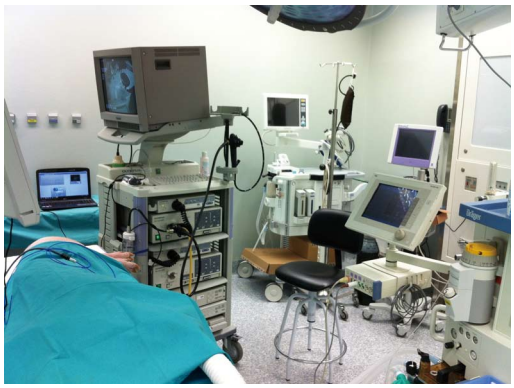

Figure 6 Operating room with equipment ready for endoscopic submucosal dissection. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

Figure 7 Freshly harvested porcine stomach (A) and rectum (B) attached inside a plastic box for *ex vivo* model. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

are easy to set, cheap and there is no need for veterinarians or anesthesia[37,40,46]. It is not acceptable to start in the live animal before being familiarized with maneuvers and the initial steps of ESD. Perforation and associated mortality are common in live animals for those novices with no experience[45]. The freshly harvested organ should be intensively cleaned before attaching the proximal esophagus to an insertion tube inside a plastic box or placing the organ in a plastic model. A similar setting has been described for porcine harvested rectum (Figure 7), with good results for CR-ESD[55]. Although these models do not reproduce real *in vivo* conditions, like spontaneous motility, bleeding and tissue reaction to injection and electrocautery, the trainee can practice special maneuvers, injection, circumferential cutting and dissection. This initial phase is a good opportunity to be familiarized with different knives and devices. Insulated knives are recommended for the naïve trainee, since non-insulated knives may be associated with a higher perforation risk[45]. It is recommended that the novice should get acceptable *en bloc* resection and perforation-free results before stepping up to live animals[48]. The general recommendation for the trainee is to initiate ESD in porcine stomach, starting in the antrum, and then progressing according to an increasingly difficult gradation to the body, the greater curvature, the lesser curvature and the fundus[43]. Afterwards, the trainee might practice in more demanding locations like the esophagus or rectum, for which a specific *ex vivo* model preparation has been described elsewhere[51,55].

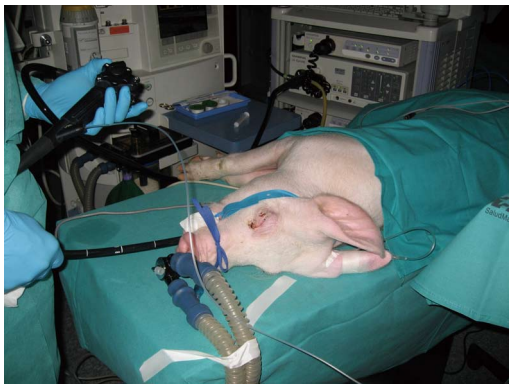

Figure 8 Gastric endoscopic submucosal dissection performed in live pig under general anesthesia. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

In vivo model

The *in vivo* model is the natural and ethically accepted next step after a sufficient period of training in the *ex vivo* model. Using live pigs requires support from veterinarians to provide preparation of the animal (24-48 h fasting is advisable), general anesthesia and euthanasia/follow-up care of the animal after procedures are completed (Figure 8). The sense of reality increases when performing ESD in live animals, with physiological reactions, including motility, mucosal secretions, bleeding and abdominal distension. In survival studies, perforation closure outcomes and post-ESD scars can be checked, which gives a chance for practicing ESD in difficult scenarios (severe fibrosis, ulceration) afterwards. This simulation can also be set up in *ex-vivo* models using banding and snare transection[56], but a more realistic approach seems to be the live animal. Once the trainee has gained enough experience in the stomach, he/she could move forward to the esophagus or the rectum and colon. Whereas the former requires a similar setting to the stomach, the rectum and colon demand an intensive preparation with bowel cleaning agents and frequently additional water infusion of the rectum[40](Figure 9).

IMPROVING YOUR SKILLS: WISE ADVICE FROM EXPERTS

There is some general advice for endoscopists already performing ESD in humans that should be kept in mind. A good field of vision and situation of the scope in relationship to the target lesion are of paramount importance. The endoscopist must know how to change the patient´s position to get the best of gravitational counter traction and a clear view to facilitate the access to the submucosal layer[57]. Managing the retroflex position ac-

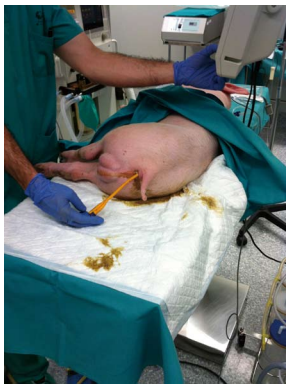

Figure 9 Preparation for rectal endoscopic submucosal dissection with intensive rectal water infusion of the rectum. Animal Research Lab. IDIPHIM. Puerta de Hierro University Hospital, Madrid, Spain.

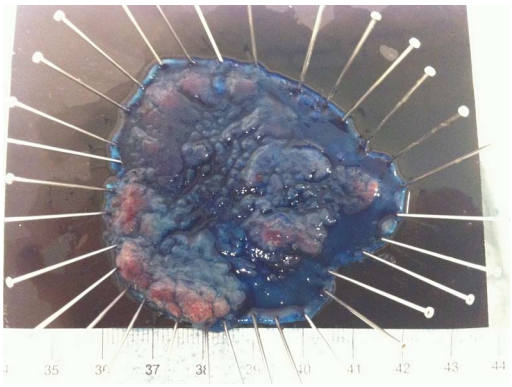

Figure 10 Colorectal-endoscopic submucosal dissection specimen fixed: LST Granular mixed type, 60 mm longest diameter located in descending colon. Puerta de Hierro University Hospital, Madrid, Spain.

curately is particularly important when performing gastric ESD, where the fundus and body locations usually require such an approach. Getting used to dissecting while positioning in such an "inverted" fashion will demand hours of hard training, ideally in the animal model setting. It has been suggested that the appropriate level for dissection is for the depth to be beneath the vascular network and above the muscle layer, so to reduce bleeding events during ESD, as well as the risk of positive vertical margin[58]. A similar recommendation is also true for lesions with severe fibrosis and, if possible, we should try to create a nice flap starting far from the lesion border. Good quality of field of vision is paramount and experienced endoscopists recommend performing a careful and systematic hemostasis of bleeding points or, even better, appropriate preventive hemostasis of visible vessels[59]. Special care should be given to the systematic coagulation of all visible vessels in the resection site after completing the resection[58]. Animal training has been essential for introducing ESD practice in Western countries[40,42], but it also plays an important role for those endoscopists engaged in human ESD who still need to increase their skills to be able to face difficult ESD locations (colon, gastric fundus *etc.*). Another aspect we should bear in mind is the great importance of preserving a complete and systematic registry of all ESD cases, so that short and long term outcomes/adverse events in our series can be analyzed[11].

COLORECTAL ESD (CR-ESD): THE HIGHEST PEAK

Although gastric ESD became a standard procedure in Japan and other Asian countries a long time ago, CR-ESD is still a challenging procedure, even for Japanese experts. Most of the experience in CR-ESD comes from large studies in Japan[34,60-62]. Eligible flat colorectal lesions for ESD are increasingly diagnosed in Japan and Western countries[63-65] and will rise even more in the near future with the expansion of colorectal screening[66,67]. Absolute indications for ESD in Japan include LST-NG > 20 mm, LST-G mixed type > 40 mm and any lesion with severe fibrosis (due to EMR, biopsies or inflammatory bowel disease)[34,60,68] (Figure 10). There is controversy regarding the adoption of CR-ESD due to the high risk of failure and complications and, since EMR appears to be good enough for the management of colorectal sessile non-invasive neoplasia[2], there are advocates for exploring alternative hybrid techniques with ESD steps associated with EMR[69].

The learning curve for CR-ESD has been analyzed in several studies. Apparently, up to 80 cases might be needed to be completed before getting excellent results (*en bloc* and R0 resection)[70]. Sakamoto *et al*[71] reported a progressive learning curve by 2 supervised trainees, reaching competence level after 30 CR-ESD. Other authors have recommended a caseload of 20 or 30 gastric ESDs before attempting CR-ESD[60,72]. It is possible that this learning curve could be reduced if additional training is completed in the animal model while performing the first human cases in the rectum, where maneuverability is easier and perforation has less impact on the patient[32]. In the learning process of CR-ESD, it might be acceptable to approach smaller lesions in the rectal location (relative indication for ESD) in order to gain experience and avoid despair[27,32].

A recent European position statement in ESD recommended steps that should be taken to acquire good skills in CR-ESD: following a progressive training, mainly in animal models, and keeping a track record[11]. There are some series of CR-ESD in European centers which show inferior outcomes, slower progression and a limitation of distal locations compared to Japanese counterparts[27,73,74]. Still, results are encouraging and a recent report showed acceptable R0 and *en bloc* resection rates in the rectum and colon after 5 and 20 cases respectively[42]. Some Japanese experts reassure us that inexperienced Western endoscopists should not try CR-ESD in lesions with significant fibrosis or larger than 40 mm during the first 30-40 cases[32].

Selected tips for CR-ESD

Adequate positioning and a high risk of perforation are the main limitations when trying to perform successful CR-ESD. You will learn from each of your cases and you should be prepared to face complications calmly to manage them and move forward. Here is some general advice for starters from my limited personal experience: (1) Ask for proper advice from experts when planning CR-ESD. It might be very useful to send pictures and/or video clips of the lesion beforehand to an expert so that you can get recommendations of whether it is eligible for ESD, suitable or not for your level of experience, tips for the approach *etc.*; (2) Consider general anesthesia for CR-ESD. You may spend many hours when approaching difficult locations and regular soft breathing moves can help you get the scope stabilized and avoid unexpected bowel movements than could facilitate an unintentional perforation. Extended deep sedation with regular drugs (propofol, midazolam, pethidine *etc.*) might induce the patient to experience intense snoring, resulting in bowel "bouncing" that makes ESD hard enough; (3) Have some rest. When performing ESD, any minor mistake can waste all your work, so it is essential to be fresh and alert. This is not easy after some hours of tense concentration, especially in the initial period of training when CR-ESD takes so long. You should consider a break after 75-90 min of a procedure when the time of reaction and concentration level may start to decline; and (4) Do record all your procedures so you are able to review your mistakes. It is especially useful to watch those moments prior to unintentional perforation so you can learn what not to do next time. Most of the time, it is a question of an excessive push of the knife or an approach in the wrong direction.

CONCLUSION

ESD is an advanced technique for early neoplasia treatment in continuous expansion, with important advantages over EMR. However, the difficult learning curve is still the main restricting factor. Training in ESD is a long and hard journey that will require comprehensive study of the ESD essentials, attending live cases, completing an animal training program using both *ex vivo* and *in vivo* models, and finally moving on to human cases under an expert´s close supervision. For Western endoscopists, this journey will be particularly arduous, with CR-ESD as the foremost challenge. And yet, most potential candidates for ESD are and probably will be colorectal early neoplasias. Intensive preparation with all available means of training is key for actual and future trainees initiating ESD. As quoted by Prof. Toyonaga, "…ESD can be a superb treatment method that is extremely beneficial for patients when the quality is well secured…"[58]. In other words, ESD in an excellent technique and there is no substitute for excellence in ESD training.

"*Never, never, never give up*" - Winston Churchill.

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MINIREVIEWS

Current status and future applications of contrast-enhanced endoscopic ultrasonography

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Abstract

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article describes the basic principles of ultrasound contrast agents and the different modalities used in contrast-enhanced EUS (CE-EUS) including contrast-enhanced Doppler EUS (CED-EUS) and contrast-enhanced harmonic EUS (CEH-EUS). In addition, the current applications of contrast enhanced EUS in different gastrointestinal conditions were discussed. Furthermore, the future development of hybrid approaches combining CE-EUS with other imaging modalities and the potential therapeutic aspect of using it as a vector for drug delivery were also discussed.

Key words: Endoscopic ultrasonography; Contrast-enhanced endoscopic ultrasonography; Advanced endoscopic ultrasonographic imaging

Core tip: This article provides a focused update on the current applications of contrast enhanced endoscopic ultrasonography in the gastrointestinal tract. Recent advances and future developments in contrast enhanced EUS are discussed.

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INTRODUCTION

Endoscopic ultrasonography (EUS) is currently an integral investigation of many gastrointestinal disorders. It has been shown to have a higher efficacy than conventional computed tomography in detection and characterization of small lesions especially in the pancreas[1]. Much effort has been put to further improve the sensitivity, specificity and overall accuracy of EUS. One of the major advances is the utilization of contrast agents for better delineation of the vascularity and tissue perfusion of the target lesion. This article aims to review the current status of contrast enhanced EUS and to provide insights into future applications of the technology in the gastrointestinal tract.

ULTRASOUND CONTRAST AGENTS

Contrast agents used in EUS are gas-containing microbubbles encapsulated in a resistant shell[2]. This shell decreases dissolution or disruption of the microbubbles in the blood stream. When hit by an ultrasonic wave, the microbubbles would oscillate and generate an acoustic signal that would be detected and reproduced on an ultrasound image[3,4]. At a low acoustic power, a nonlinear return signal containing multiples of the resonating frequency would be detected[5]. These higher frequency components, known as harmonics, are fundamental to the "enhancement" detected when performing contrast-enhanced harmonic ultrasonography[6].

Three generations of ultrasound contrast agents have been developed based on their capability of transpulmonary passage and half-life in the human body (Table 1)[7]. First generation agents are microbubbles filled with air, but they generally require high acoustic power to produce oscillation or break its microbubbles. Second generation agents, including the commonly used SonoVue™ and Sonazoid™, are composed of gases that are less soluble and less likely to leak out from microbubbles, thereby lasting longer in the circulation. These agents can be oscillated or broken by lower acoustic power, and thus are more suitable for EUS because of the limited acoustic power produced by the small transducer. Third generation agents (Echogen™) are capable of phase shifting from liquid to gas form once they reach body temperature. These agents are not widely used in EUS of the gastrointestinal tract as yet. Ultrasound contrast agents are generally safe, and adverse reactions are rarely observed. The macromolecules within the agent could lead to allergic reactions, which mostly are mild. There is also minimal clinical significance regarding the toxic or embolic potential and biological effects of these ultrasound contrast agents[5].

Table 1 Contrast agents for ultrasonography[7]

Contrast agent	Composition	Manufacturer
First generation		
Albunex	5% Sonicated serum albumin with stabilized microbubbles	Mallinckrodt
Echovist (SHU 454)	Standardized microbubbles with galactose shell	Schering
Levovist (SHU 508)	Stabilized, standardized microbubbles with galactose, 0.1% palmitic acid shell	Schering
Myomap	Albumin shell	Quadrant
Qantison	Albumin shell	Quadrant
Sonavist	Cyanoacrylate shell	Schering
Second generation		
Definity/ luminity	C3F8 with lipid stabilizer shell	Bristol-Myers Squibb Medical Imaging
Sonazoid	C4F10 with lipid stabilizer shell	GE Healthcare
Imagent-Imavist	C6F14 with lipid stabilizer shell	Alliance
Optison	C3F8 with denatured human albumin shell	GE Healthcare
Bisphere/ carbiosphere	Polylactide-coglycolide shell with albumin overcoat	Commercially unavailable
SonoVue	SF6 gas with lipid stabilizer shell	Bracco
AI700/imagify	C4F10 gas core stabilized with polymer shell	Acusphere
Third generation		
Echogen	Dodecafluoropentane (DDFP) liquid in phase shift colloid emulsion	Sonus Pharmaceuticals

CATEGORIES OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

After intravenous contrast injection, sonographic assessment of the target of interest could be performed by two methods: contrast enhanced color/power Doppler imaging (CED-EUS) and contrast enhanced harmonic imaging (CEH-EUS). Contrast injection in conventional B-mode ultrasound is not recommended as it would not improve imaging quality and the detection of contrast agents is poor in the presence of surrounding tissue. When contrast agents are used with Doppler EUS, it would allow detection of intratumoral vessels with enhancement of tumor vascularity[8-14]. However, vessels with slow flow are still poorly depicted, as this mode has a low sensitivity to low blood flow[6,9,15]. Blood flow from surrounding vessels can also create motion and blooming artifacts, increasing the difficulty in evaluation of tumor vascularity. Motion artifacts refer to low signal intensity of flowing blood when compared to that of tissue movement, while blooming artifacts refer to the widened appearance of a blood vessel with power Doppler[6].

CEH-EUS was recently developed to overcome the difficulties experienced with Doppler EUS. As mentioned above, the harmonic component refers to the return signal of multiples of the fundamental frequency. The harmonic component derived from microbubbles is higher than that from tissues, and the harmonic imaging technique detects these signals. It also filters signals that originate from the tissue by selectively detecting the harmonic components, thereby producing images that depict vessels with very slow flow without Doppler related artifacts[6].

Dietrich *et al*[16] first reported the use of CEH-EUS in 2005. In their study, they demonstrated the possibility of arterial, portal venous and parenchymal contrast enhancement after injection of a second generation contrast agent. Kitano *et al*[17,18] also reported their initial experience with a novel echoendoscope (XGF-UCT260W; Olympus Medical Systems Co. Ltd., Tokyo, Japan) that was equipped with a broadband transducer and extended pure harmonic detection mode. Pancreatic parenchymal perfusion and branching vessels were only observed after contrast injection with the harmonic mode but not the power-Doppler mode, enabling further improvement in accuracy of assessment of tissue vasculature (Figure 1). Since then, numerous studies have reported the use of this novel technique for assessment of different gastro-

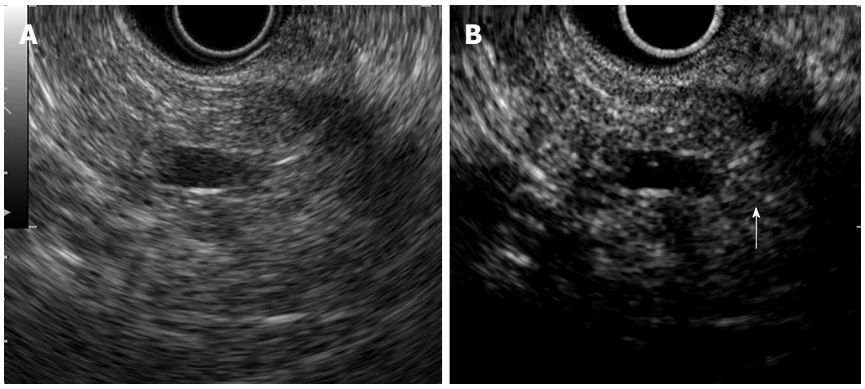

Figure 1 Contrast-enhanced harmonic-endoscopic ultrasonography images of pancreatic parenchymal perfusion. A: Conventional B-mode image; B: Contrast-enhanced harmonic image. Arrowhead indicates pancreatic parenchyme with small vasculature.

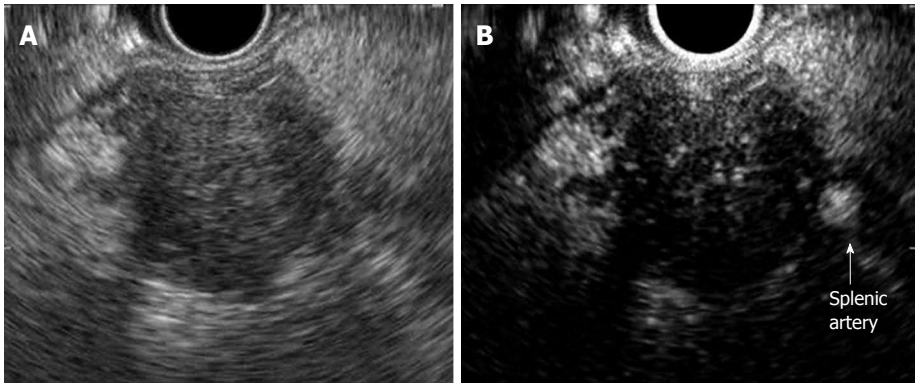

Figure 2 Hypoenhancing pancreatic tumour. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

intestinal and pancreatic pathologies. However, inter-observer agreement of CEH-EUS was only found to be fair to moderate[19]. Upon a review of 80 EUS videos by 15 endosonographers, overall inter-observer agreement was moderate for the uptake of contrast agents (k = 0.567) and fair for the pattern of distribution (k = 0.304) and the washout velocity (k = 0.369). This finding highlighted a major limitation of the technique that qualitative image analysis of contrast enhanced images is subjected to individual interpretation.

CURRENT APPLICATIONS OF CONTRAST-ENHANCED EUS

Pancreatic solid lesions

Differentiation between pancreatic ductal carcinoma and other pancreatic pathologies such as autoimmune pancreatitis and neuroendocrine tumors is difficult by conventional EUS. By CEH-EUS, four types of enhancement patterns have been reported previously: non-enhancement, hypo-enhancement, iso-enhancement and hyper-enhancement[20]. Hypo-enhancement pattern has been identified as the most common distinguishing feature of pancreatic adenocarcinoma (Figure 2). A recent meta-analysis including studies of both contrast enhanced Doppler EUS and contrast enhanced harmonic EUS reported an overall high sensitivity of 94% (95%CI: 0.91-0.95) and specificity of 89% (95%CI: 0.85-0.92) in diagnosing pancreatic adenocarcinoma[21-26]. Kitano *et al*[20] reported the largest series of 277 patients with solid pancreatic lesions who underwent contrast enhanced harmonic EUS with Sonazoid™. When compared with multi-detector contrast enhanced computed tomography, CEH-EUS yielded a significantly higher accuracy in diagnosing pancreatic adenocarcinomas that were less than 2 cm in size, with a sensitivity of 91.2% (95%CI: 82.5-95.1) and specificity of 94.4% (95%CI: 86.2-98.1). Furthermore, CEH-EUS was also superior in predicting the T-stage of pancreatobiliary tumors as compared with conventional EUS. In particular by CEH-EUS, the wall of the portal vein was better depicted, enabling better visualization of portal vein invasion and providing valuable information for surgical planning for vascular resection[27]. In patients with unresectable carcinoma of the pancreas, CEH-EUS has also been demonstrated to aid in predicting efficacy of chemotherapy. The presence of intratumoral vessels predicted a better progression free and overall survival after chemotherapy[28].

On the other hand, a hyper-enhancing pattern was identified to be a common feature in pancreatic neuroendocrine tumors (PNETs), with a sensitivity of 78.9% and a specificity of 98.0%[20] (Figure 3). The presence of filling defects within an enhancing pancreatic lesion cor-

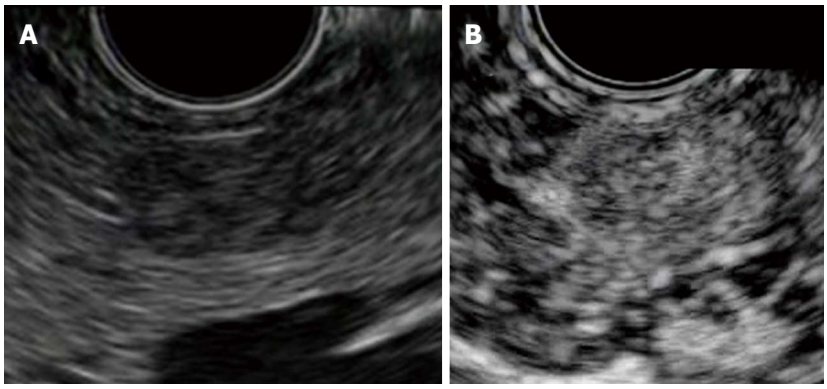

Figure 3 Hyperenhancing pancreatic insulinoma. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

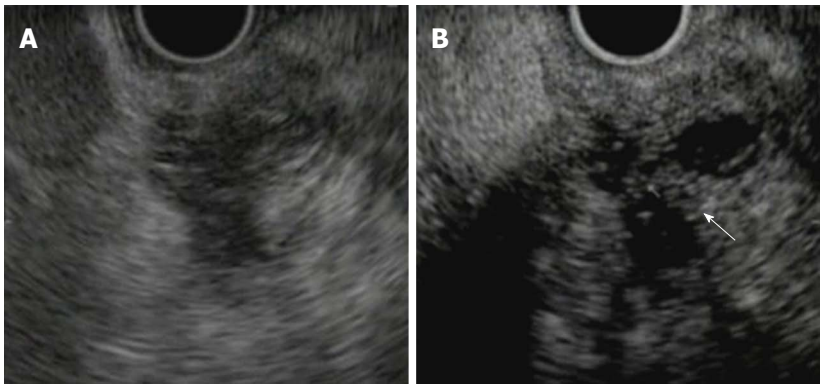

Figure 4 Contrast enhancing mural nodules of a pancreatic cystic neoplasm. A: Conventional B-mode image. B: Contrast-enhanced harmonic image. Arrow indicates mural nodule.

responded to hemorrhage or necrosis of malignant diseases as seen on pathological examination. This may have a potential role in differentiating benign versus malignant PNETs[13].

Pancreatic cystic lesions

The differentiation between benign and malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas is difficult. Mural nodules have been identified as one of the most important indicator in the prediction of malignancy. A study published in 2009 demonstrated the ability of contrast enhanced EUS in characterizing mural nodules found in IPMNs[29] (Figure 4). Mural nodules were classified into four types based on the CE-EUS findings, and types Ⅲ (papillary nodule) and Ⅳ (invasive nodule) patterns were more frequently associated with invasive cancer, at 88.9% and 91.7%, respectively. A subsequent series by the same group of authors also found that only CE-EUS identified the presence of mural nodules in 27.3% of cases with proven malignant IPMNs after surgical resection[30]. Accurate differentiation between true mural nodules from mucous clots could also be achieved by contrast enhanced EUS[31].

Gastrointestinal stromal tumors

In a study of 17 patients with gastro-esophageal submucosal lesions, CEH-EUS was able to differentiate between gastrointestinal stromal tumors (GISTs) and other benign submucosal tumors such as leimyoma or lipoma by the pattern of contrast enhancement[32]. All 9 histologically proven GISTs showed hyperenhancement after contrast injection.

CEH-EUS has also been utilized to differentiate between low grade versus high grade malignant GISTs. In a study by Sakamoto *et al*[33], two distinctive vascular patterns were identified by CEH-EUS. Type Ⅱ pattern demonstrating irregular vessels on vessel image and heterogeneous enhancement on perfusion image was more commonly found in high grade malignant GISTs (Figure 5). The overall sensitivity, specificity and accuracy in prediction of malignant risk were 100%, 63% and 83%, respectively. A significantly higher sensitivity of CEH-EUS in detecting intra-tumoral vessels among high-grade malignant GISTs was also demonstrated when compared with multidetector computed tomography (CT) and power-Doppler EUS.

Gallbladder and bile duct lesions

The utilization of CEH-EUS in differentiating cholesterol polyps, gallbladder adenoma and gallbladder carcinoma has been studied. The sensitivity and specificity of CEH-EUS for differential diagnosis of gallbladder adenoma and cholesterol polyps based on the enhancement pattern were 75.0% and 66.6%, respectively, according to a study

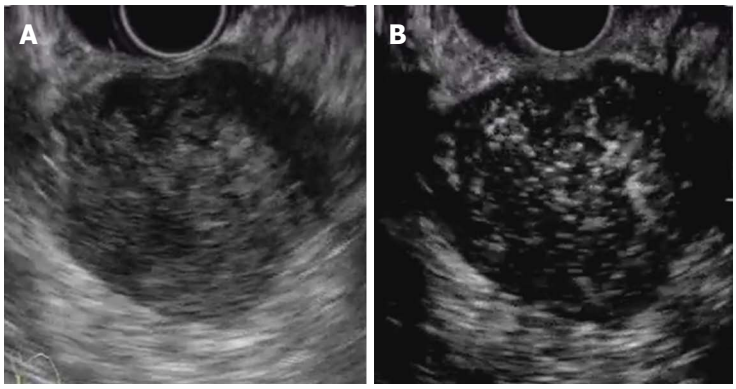

Figure 5 Heterogeneous enhancement with perfusion defects present in high grade gastrointestinal stromal tumors. A: Conventional B-mode image; B: Contrast-enhanced harmonic image.

by Park *et al*[34]. In another study of 93 gallbladder polyps > 1 mm, identification of irregular intratumoral vessels and perfusion defect aided in diagnosing malignant from benign gallbladder polyps, with a sensitivity of 93.5% and a specificity of 93.2%[35].

Bile duct thickening is a common feature in both benign and malignant biliary conditions such as primary or secondary sclerosing cholangitis and bile duct carcinoma. Studies have shown that contrast enhancement in the bile duct wall corresponds to non-neoplastic changes of the bile duct as in cholangitis[36,37].

Intra-abdominal lesions of undetermined origin

Contrast enhanced EUS has been found to be useful in differentiating benign versus malignant intra-abdominal lesions of unknown origin. In a study published by Xia *et al*[38], 43 patients with such a condition underwent CEH-EUS. Correlating with FNA results, the differentiation of malignancy was made by identifying heterogeneous enhancement within these lesions, with a sensitivity, specificity and accuracy of 96.3%, 100% and 97.6%, respectively. Of note, most lesions in the series were indeed intra-abdominal lymphadenopathies with benign or malignant changes.

Visceral vascular assessment

In a small study of 12 patients, all visceral vascular lesions were accurately diagnosed by the use of combined Doppler and CEH-EUS, including one undefined lesion by abdominal CT. The findings of EUS helped determine the appropriate intervention without radiation exposure[39].

Contrast enhanced EUS has also been utilized in other upper gastrointestinal diseases, including the depth of invasion in gastric carcinoma[40] and hemodynamic assessment of esophageal varices[41,42].

FUTURE DEVELOPMENT OF CONTRAST ENHANCED ENDOSCOPIC ULTRASONOGRAPHY

As stated previously, contrast enhanced EUS has been criticized for its qualitative nature. Quantitative methods have been proposed to improve the reliability. Two groups of authors reported the results with time intensity curve (TIC) of contrast uptake in differentiating pancreatic diseases[43,44]. According to Matsubara and colleagues, pancreatic carcinoma, in contrast to other pancreatic pathologies, yielded the greatest echogenic intensity reduction rate from the peak at 1 min after contrast injection. The diagnostic accuracy of EUS in combination with TIC reached 94.7% in their study[44].

A hybrid approach combining EUS with other imaging modalities has also been investigated recently. It was based on electromagnetic position tracking of the EUS transducer position and co-registration with a planar reconstructed image from those obtained on CT or magnetic resonance imaging[45,46]. A preliminary study has demonstrated that estimation of tumor angiogenesis through combining different imaging modalities was possible[47]. It may also increase the diagnostic accuracy through direct comparison of the target lesion by different imaging techniques. Furthermore, improved selection and enhanced visualization are possible for EUS guided FNA of lesions that are not clearly visible in the EUS field[48]. Contrast enhanced EUS could also help determine the likelihood of a false negative FNA result for pancreatic solid lesions.

The therapeutic potential of contrast enhanced ultrasonography has also been explored. Drug substances, such as plasmid DNA, could be delivered within the microbubbles of ultrasound contrast agents. Upon exposure to ultrasonic waves with very high acoustic power, rapid disintegration of microbubbles would occur and the drug within the microbubbles could be released. When combined with endoscopic ultrasound, the technique may aid in targeted drug delivery in pancreatic tumors[5,49,50].

CONCLUSION

With the recent advances in contrast enhanced EUS and CEH-EUS, better characterization of different gastrointestinal pathologies could be achieved. Furthermore, contrast enhanced EUS could play an increasingly important role in diagnosis and management of these conditions in

the future.

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ORIGINAL ARTICLE

Accuracy of transnasal endoscopy with a disposable esophagoscope compared to conventional endoscopy

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Abstract

AIM: To assess feasibility of unsedated esophagoscopy using a small-caliber disposable transnasal esophagoscopy and to compare its accuracy with standard endoscopy.

METHODS: We prospectively included subjects who were referred for upper endoscopy. All subjects underwent transnasal endoscopy with E.G. Scan™. The disposable probe has a 3.6 mm gauge and at its distal end there is a 6 mm optical capsule, with a viewing angle of 125°. Patients underwent conventional endoscopy after the completion of E.G. Scan™. We describe the findings detected by the E.G. Scan™ and calculate the diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value and Kappa index for esophageal diagnosis.

RESULTS: A total of 96 patients (54 women), mean age of 50.12 years (14 to 79), were evaluated. In all cases we were able to perform esophagoscopy with E.G. Scan™. The average realization time was 5 min. A total of 58 alterations were detected in the esophagus, 49 gastric abnormalities and 13 duodenal abnormalities. We found that for esophageal varices, E.G. Scan™ has sensitivity, specificity and diagnostic accuracy of 95%, 97% and 97%, respectively. Kappa coefficients were 0.32 for hiatal hernia, 0.409 for erosive gastroesophageal reflux disease, 0.617 for Barrett's esophagus, and 0.909 for esophageal varices.

CONCLUSION: Esophagoscopy with E.G. Scan™ is a well-tolerated, fast and safe procedure. It has an appropriate diagnostic accuracy for esophageal varices when compared with conventional endoscopy.

Key words: Esophagoscopy; Esophagus; Transnasal; Endoscopy

Core tip: Although esophagogastroduodenoscopy (EGD) is considered the gold standard technique for evaluation of mucosal esophageal diseases, the cost and invasiveness of this diagnostic tool limits its utilization in some patients. Thus, in recent years several endoscopy techniques have been developed as alternatives and less invasive diagnostic tools for evaluating gastroesophageal reflux disease and esophageal varices. Here, in this study we have shown that unsedated esophagoscopy using a novel disposable transnasal esophagoscope (E.G. Scan™) is a safe, well-tolerated, effective and accurate screening tool for esophageal diseases, specifically for esophageal varices.

Aedo MR, Zavala-González MÁ, Meixueiro-Daza A, Remes-Troche JM. Accuracy of transnasal endoscopy with a disposable esophagoscope compared to conventional endoscopy. *World J Gastrointest Endosc* 2014; 6(4): 128-136 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/128.htm DOI:

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is the most effective method to investigate disorders affecting the upper digestive tract. In particular, EGD is the gold standard technique for the evaluation, diagnosis, screening and surveillance of esophageal diseases. Among patients with gastroesophageal reflux disease (GERD) symptoms, up to one-third of patients have endoscopic evidence of erosive esophagitis and up to one-fifth have complicated reflux disease, such as esophageal strictures and Barrett's esophagus (BE)[1,2]. In subjects with portal hypertension, EGD is used for both screening and surveillance purposes because the presence and the size of esophageal varices correlates with severity of liver disease and determines the prognosis[3,4].

Although EGD is widely used and available, the procedure is costly, may be unpleasant, and still has a small but potential risk of complications[5,6]. Frequently, patients are routinely sedated with intravenous diazepam or midazolam, often complemented with a narcotic such as meperidine, fentanyl or propofol[6]. There is a small but definite risk of cardiopulmonary complications, which may be related to a combination of oversedation and pre-existing cardiopulmonary disease[6]. In addition, sedated patients require close monitoring during and after procedures, cannot drive or return to work on the day of the procedure, and may have post-procedure amnesia with poor recall of instructions.

Over the last years, several noninvasive or minimally invasive methods have been proposed as alternatives to conventional EGD for the diagnosis of esophageal diseases, such as esophageal capsule endoscopy (ECE) and ultra-thin small caliber esophagoscopes[7-12]. Several studies have shown that ECE is safe and has an acceptable accuracy for the evaluation of esophageal varices and can be used as an alternative to EGD for the screening of portal hypertension, especially in patients unable or unwilling to undergo EGD[7,9].

Unsedated small-caliber transnasal esophagoscopy offers the possibility of efficient and accurate endoscopic assessment of the esophagus, with less cost and fewer risks compared with sedated upper endoscopy, and can be used as a method to screen for esophageal disease in a primary care population[11-15]. Recently, Chung *et al*[16], in a case series study, reported the use of a novel disposable transnasal esophagoscope, the E.G. Scan™ (IntroMedic Co. Ltd., Seoul, South Korea). This transnasal esophagoscope does not require a large endoscopy system or special equipment for disinfection; it is portable, disposable and well tolerated.

The aim of the study was to assess the feasibility of unsedated routine upper esophagoscopy using the E.G. Scan™ and to compare its optical quality and diagnostic accuracy to that of a standard EGD in the general medical outpatient setting as a screening method for esophageal disease.

MATERIALS AND METHODS

Patients

We performed a prospective study conducted from November 2011 to February 2012 at the Instituto de Investigaciones Medico Biologicas de la Universidad Veracruzana, Veracruz, México. Consecutive patients referred for the evaluation of esophageal diseases were enrolled in the study. Inclusion criteria were: age 20 years or older; reflux symptoms (heartburn, epigastric soreness and/or regurgitation); non-cardiogenic chest pain; and known or suspected esophageal varices. Exclusion criteria included: history or symptoms of severe rhinitis and sinusitis; acute respiratory inflammation at the time of examination; and known abnormal anatomy of the nasal cavity or nasopharynx. All patients provided written informed consent before enrollment and the study received approval from the institution's ethics committee.

Procedures

All conventional EGD and E.G. Scan™ procedures were performed by two experienced endoscopists (J.M.R.T. and A.M.D) after written informed consent was obtained. Randomization was performed by using a computer-generated randomization (www.randomization.com), which allocated patients on a one-to-one basis to the investigator who will perform the EG Scan procedure. Thus if one investigator performed the E.G. Scan™, the other performed the conventional EGD, and investigators were blinded each other. Also, endoscopists were blinded to the indication for endoscopy. The E.G. Scan™ procedure was performed first and 45 min later a conventional sedated endoscopy was performed.

E.G. Scan™: After an overnight fast, patients were referred to the endoscopy unit. For the procedure, patients were seated with their neck at a 30° angle and 2 puffs of a nasal spray containing oxymetazoline hydrochloride, a selective alpha-1 agonist and partial alpha-2 agonist topical nasal decongestant, was sprayed in each nostril (Afrin, Merck Consumer Care, Inc. Mexico). After 5 min, lidocaine hydrochloride 10mg/dose (Xylocaine 10% Pump Spray AstraZeneca, London, United Kingdom) was sprayed into the nasal cavity and oropharynx for topical anesthesia. The endoscope, moistened with Lidocaine HCL jelly 2% (lidocaine hydrochloride 2% 20 mg/mL; Lubricaine, Mexico), was inserted under visual control through the nostril to the pharynx. Upper esophageal sphincter intubation was facilitated by asking the patient to ingest water through a straw with endoscope advancement. No sedatives or antispasmodics were used during the procedure.

The E.G. Scan™ system (first generation) consists of four main subsystems: a probe (containing the camera capsule, bending module and data connector), control-

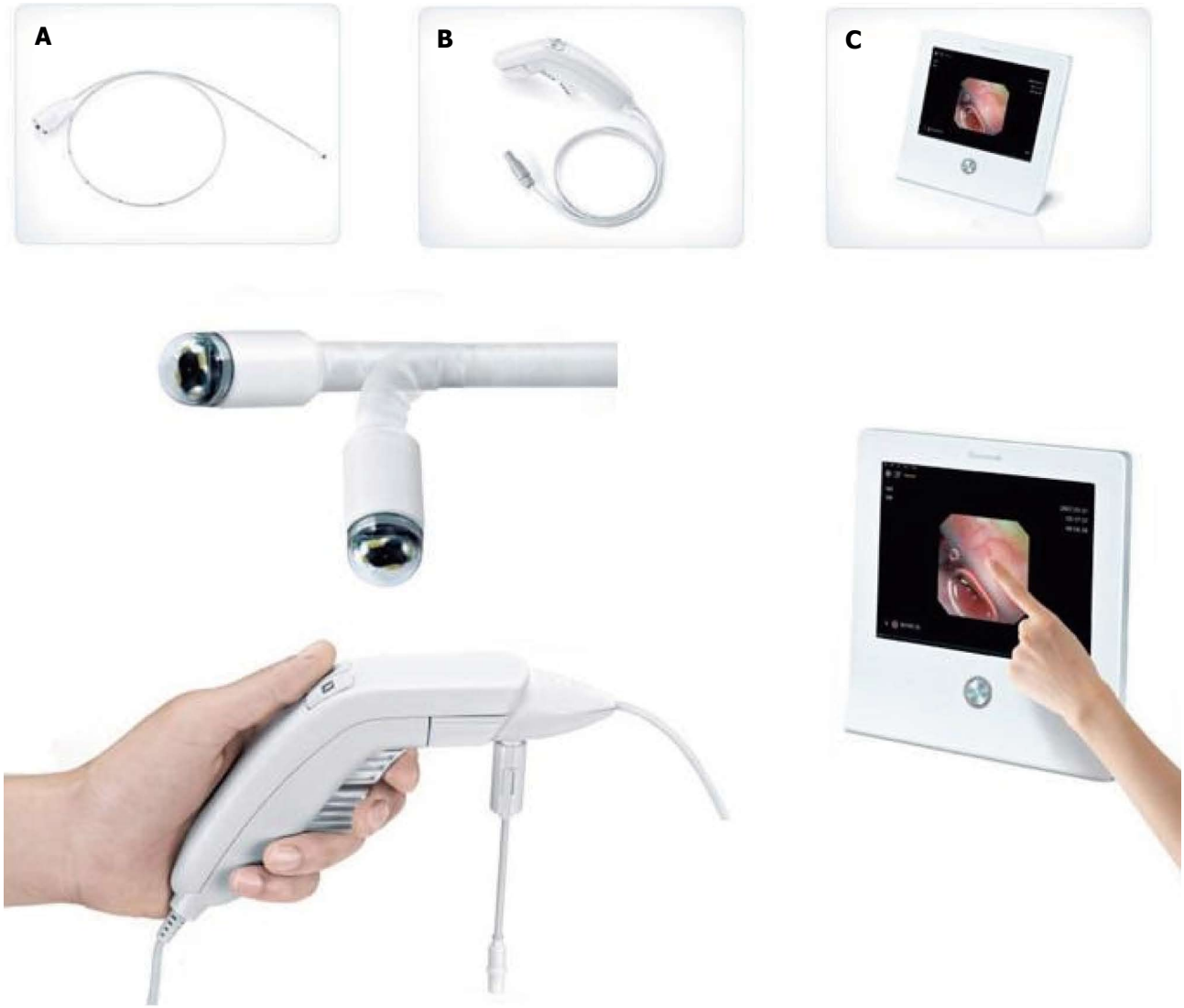

Figure 1 Components of the E.G. Scan™ system (first generation). A: A probe containing the camera capsule, bending module and data connector; B: A controller; C: A display system with computer software to display the images (E. G. View™).

ler, display system and computer software (EG View) to display the images (Figure 1). The connection tube, which does not have suction or an air channel, is 3.6 mm in diameter and the camera capsule at the tip head is 6 mm in diameter. The tip deflection capability is 60° up and 60° down. The camera capsule comprises four white light emitting diodes (LEDs) and a complementary metal-oxide semiconductor (CMOS), with a field of view of 125° and a resolution of 400 × 400 pixels. The probe is disposable. The controller has both freeze-capture buttons and an up-down lever at the handle. The display system consists of a liquid crystal display (LCD) monitor, keyboard and display software (EG View) to allow playback and storage of images taken during the procedure; this system is light enough to carry.

During the procedure, the posterior pharynx, esophagus, esophagogastric junction (EGJ) and proximal stomach were routinely examined. EGJ examination was considered appropriate if at least 75% of the Z-line was visualized[16]. If possible, the mid-stomach, pylorus and duodenum were examined. Any pathological lesions were photographed and recorded on the display system. The investigators documented the duration time of the study, presence or absence of suspected BE, presence or absence of erosive esophagitis, Los Angeles grade of erosive esophagitis (if present), presence or absence of hiatal hernia (documented and measured at the nares in centimeters beginning at the crural pinch distally to the most proximal extent of the gastric folds), esophageal varices were graded according to the size of varices (small or large), the presence or absence of red spots on esophageal varices was also noted, and any other abnormal findings discovered during the study. These findings were recorded on a data sheet. After the procedure, patients completed a written questionnaire to assess their satisfaction with the E.G. Scan™ and level of discomfort for nasal pain and nausea using a 4 point type Likert scale (0 = none, 1 = mild, 2 = moderate and 3 = severe)[17,18].

EGD: Sedated endoscopy was performed with the

Table 1 Baseline characteristics and symptoms *n* (%)

Age (yr, mean, range)	50.12 (18-79)
Gender (male/female)	42/54
Predominant symptoms	
Reflux symptoms	41 (43)
Suspect of esophageal varices	23 (24)
Epigastric pain	14 (15)
Upper GI bleeding	11 (11)
Dysphagia	4 (4)
Weight loss	3 (3)

GI: Gastrointestinal.

Olympus XGIF-160 with patients under local anesthetic with lidocaine spray (Xylocaine; AstraZeneca, United Kingdom) and conscious sedation with midazolam, according to our standard practice. Blood pressure, pulse, cardiac rhythm and oxygen saturation were monitored and recorded every 2 min. In all cases, the endoscope was inserted under visual control through the mouth to the pharynx. The upper esophageal sphincter was crossed under direct vision and the esophagus, stomach and first and second portions of the duodenum were examined as usual. Endoscopic findings were reported using the definitions previously mentioned. Histological confirmation of esophageal biopsies from endoscopically suspected esophageal metaplasia was considered as the "gold standard" for the diagnosis of BE.

Statistical analysis

EGD was considered to be the "gold standard" for the diagnosis of esophageal diseases. According to the Standards for Reporting of Diagnostic Accuracy (STARD) initiative on assessment of diagnostic tests[19], analysis was performed on an intention-to-diagnose (ITD) basis, with all patients enrolled in the trial included in the analysis. The diagnostic performance was expressed in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

At the end of the enrollment period and in a blinded fashion, both endoscopists reviewed the printed images from all E.G. Scan™ studies and interobserver agreement analysis was performed. Concordance among the different E.G. Scan™ observers and between the E.G. Scan™ and EGD final diagnoses was performed using kappa statistics. Our sample size was decided arbitrarily, according to the available material to perform the studies (E.G. Scan™) during the frame time when the study was performed. All other statistics were descriptive and the results are reported in terms of the mean (with 95% confidence interval in brackets) or median and ranges, depending on the distribution of data values. *P* values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of patients at baseline

During the study period, a total of 96 patients (54 women) were included. Mean age was 50.12 years (range 18 to 79). Baseline characteristics and symptoms are described in Table 1. In all cases, we were able to perform esophagoscopy with E.G. Scan™ and the mean duration of the procedure was 5 min (range 3-7.5).

Table 2 E.G. Scan™ and conventional endoscopy esophageal findings

Finding	E.G. Scan™	Conventional EGD
Esophagus		
Esophageal varices (overall)	20	21
Small	5	8
Large	11	13
Erosive GERD	13	29
Grade A-B	10	20
Grade C	2	8
Grade D	1	1
Hiatal hernia	13	33
Barrett's esophagus	8	12
Esophageal carcinoma	2	2
Esophageal angiodysplasia	1	1
Gastric heterotopic mucosa	1	1

EGD: Esophagogastroduodenoscopy; GERD: Gastroesophageal reflux disease.

E.G. Scan™ evaluation

Using the E.G. Scan™ in all cases, the EGJ was evaluated; in 43% the pylorus was visualized and we reach the duodenum in 36% cases. Appropriate evaluation of the EGJ junction was achieved in 95% (n = 91). A total of 58 alterations were detected in the esophagus (Table 2), 49 gastric abnormalities (18 portal hypertension gastritis, 18 mild erythematous gastritis, 10 bile gastropathy, 3 gastric polyps) and 13 duodenal abnormalities (9 duodenitis, findings suggestive of celiac disease in 2, 1 duodenal ulcer and 1 angiodysplasia) (Figures 2-5).

Conventional EGD

Using conventional endoscopy, a total of 99 esophageal diagnoses were made (Table 2). In addition, 71 gastric abnormalities were detected (23 portal hypertension gastritis, 21 erythematous and/or erosive gastritis, 15 bile gastropathy, 8 fundic polyps and 4 fundic varices), and 25 duodenal abnormalities (19 duodenitis, 3 findings suggestive for celiac disease and 3 duodenal ulcers).

Comparison of E.G. Scan™ and EGC

The diagnostic performance of E.G. Scan™ compared to EGD for erosive GERD, Barrett's esophagus, esophageal varices and hiatal hernia is shown in Table 3. Regarding the agreement between E.G. Scan™ and EGD, the kappa values for esophageal diagnoses is shown in Table 4.

E.G. Scan™ interobserver agreement

The mean kappa values for interobserver agreement for each esophageal condition were: for hiatal hernia 0.762 (0.506-1.018); for erosive esophagitis 0.832 (0.606-1.058); for BE 0.554 (0.207-0.901); for esophageal varices 0.903 (0.796-1.011); for large esophageal varices 0.911

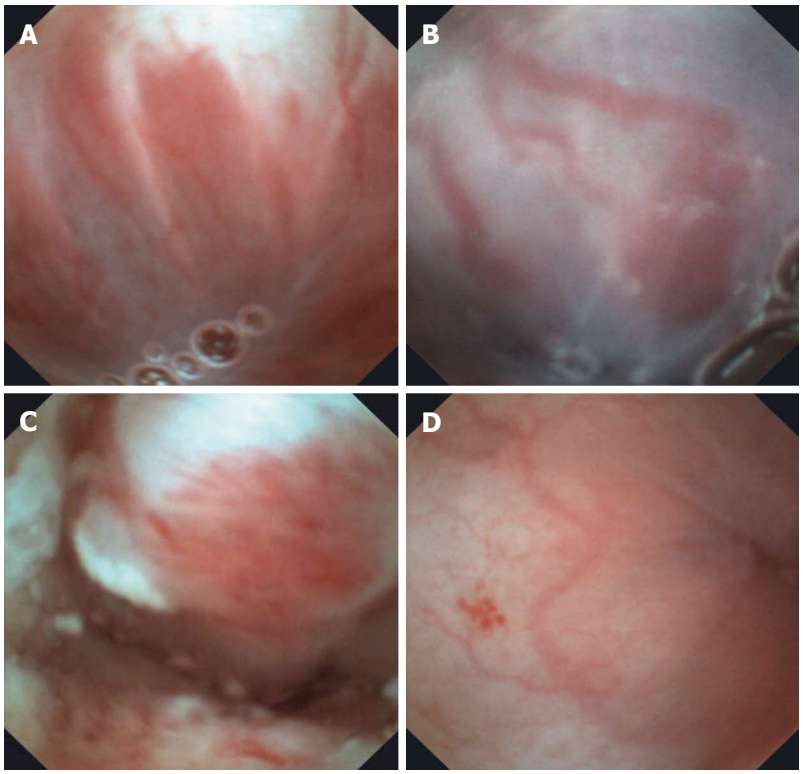

Figure 2 Examples of esophageal diseases detected with the E.G. Scan™. A: Large esophageal varices; B: Medium-small esophageal varices; C: Distal esophageal adenocarcinoma; D: Esophageal angiodysplasia.

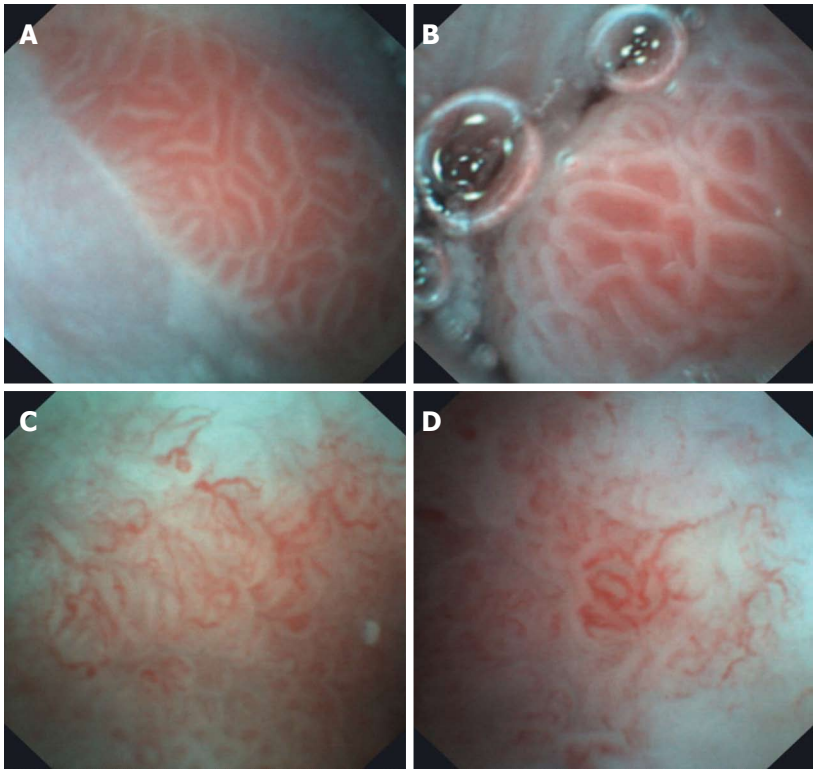

Figure 3 Barrett's esophagus images obtained with E.G. Scan™. A and B: Barrett's without dysplasia; C and D: Barrett's esophagus with low-grade dysplasia.

(0.739-1.083); and for small esophageal varices 0.832 (0.606-1.058).

Patient tolerance

Nasal introduction caused no or only mild pain in 77 of

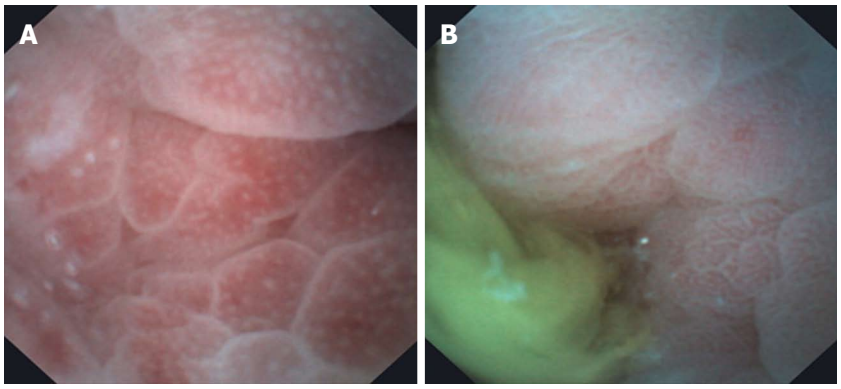

Figure 4 Gastric images obtained with E.G. Scan™. A: Portal hypertension gastropathy; B: Bile reflux gastritis.

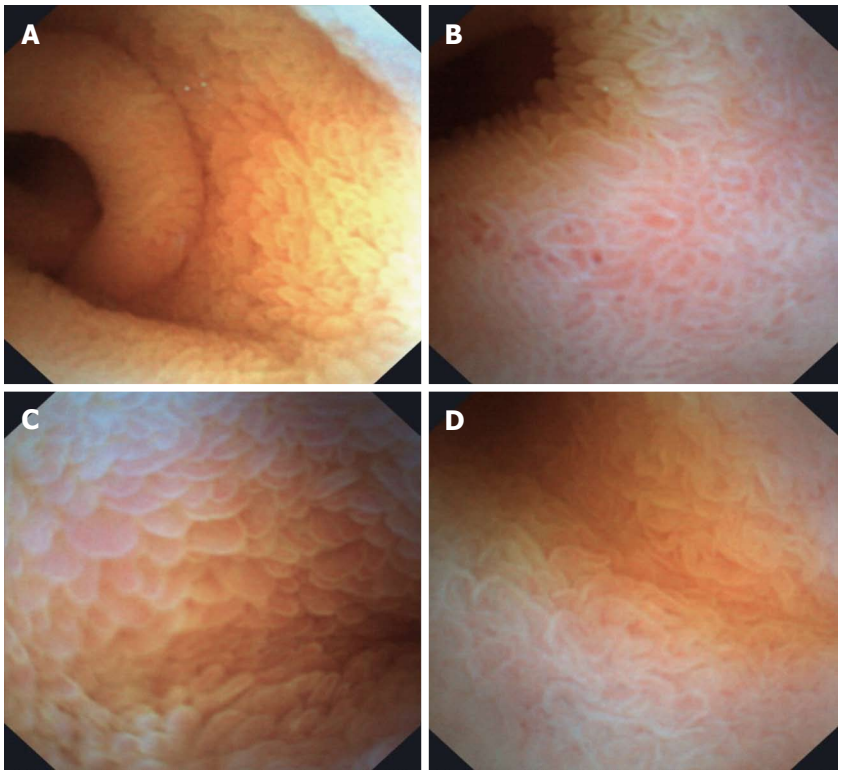

Figure 5 Duodenal images obtained with E.G. Scan™. A: Normal duodenum; B: Mild duodenitis; C and D: Celiac disease.

96 patients (80%) and moderate pain in 19 patients (20%). The majority of patients did not experience nausea (88%).

DISCUSSION

Although EGD is considered the gold standard technique for evaluation of mucosal esophageal diseases, the cost and invasiveness of this diagnostic tool limits its utilization in many patients[6]. Thus, several endoscopy techniques have recently been developed as alternatives and less invasive diagnostic tools for evaluating GERD and esophageal varices[12-16,20].

Here, in this study we have shown that unsedated esophagoscopy using a novel disposable transnasal esophagoscope (E.G. Scan™) is a safe, well-tolerated, effective and accurate screening tool for esophageal diseases, specifically for esophageal varices. In recent years, the use of transnasal endoscopy (TNE) has had a boom and several studies have evaluated the usefulness of this technique. For example, Peery *et al*[20] in one of the largest studies (n = 426) found that TNE is a safe and good method to screen for esophageal disease in a primary care population. In this study, mean examination time with TNE was 3.7 ± 1.8 min and there were no serious adverse events. Our results are similar, but the E.G. Scan ™ has some advantages compared to other transnasal endoscopy systems. Although the tip of the probe is 6 mm in diameter, the connection tube (which does not have suction or an air channel) is 3.6 mm in diameter; thus, the probe is smaller than other TNE (range from 4.1 to 5.9 mm) and could minimize the gag reflex and vomiting. Another advantage is that no disinfection is required be-

Table 3 Diagnostic performance of E.G. Scan™ compared to conventional esophagogastroduodenoscopy

	Prevalence % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Accuracy % (95%CI)
Erosive GERD	30.1 (21.5-40.6)	44.8 (27-64)	91 (80.9-96.3)	68.4 (43.5-86.4)	79.2 (68.2-87.3)	77.1 (67.2-84.8)
Barrett's esophagus	12.5 (6.9-21.2)	66.7 (35.4-88.7)	95 (87.6-98.5)	66.7 (35.4-88.7)	95.2 (87.6-98.5)	91.7 (83.8-96.1)
Esophageal varices	21.8 (14.4-31.7)	95.2 (74.1-99.8)	97.3 (89.8-99.5)	90.9 (69.3-98.4)	98.6 (91.7-99.9)	96.8 (90.5-99.1)
Hiatal Hernia	34.4 (25.1-44.8)	39.4 (23.4-57.7)	88.9 (77.8-95)	65 (41-83.7)	73.7 (62.1-82.8)	71.9 (61.6-80.3)

PPV: Positive predictive value; NPV: Negative predictive value; GERD: Gastroesophageal reflux disease.

Table 4 Kappa values for esophageal diagnosis E.G. Scan™ *vs* esophagogastroduodenoscopy

	Kappa value	Standard error of Kappa	95%CI
Esophageal varices	0.910	0.051	0.810-1.010
Large esophageal varices	0.822	0.086	0.653-0.911
Small esophageal varices	0.591	0.151	0.294-0.880
Barrett's esophagus	0.619	0.123	0.378-0.860
Hiatal Hernia	0.398	0.103	0.196-0.600
Erosive esophagitis	0.398	0.100	0.196-0.600

cause the probe is designed for single use and is disposable.

Chung *et al*[16], in the first study published with E.G. Scan™, evaluated 46 patients with suspected or known esophageal disease and found that in almost all cases, the Z line was appropriately evaluated and abnormalities were identified in 27 patients. In this small sample size pilot study, the authors concluded that although E.G. Scan ™ has some technical limitations compared with conventional EGD, its convenience, good tolerance, rapid access, cost-effectiveness and good safety profile indicate that it may be an acceptable alternative to conventional esophagoscopy for surveillance.

Compared to the pilot study by Chung *et al*[16], our study included a larger sample size, we performed the first randomized and blinded evaluation, but most remarkably, we compared the results with the gold standard technique, the EGD. Because conventional endoscopy with sedation may be associated with complications, especially in critically ill patients such as subjects with cirrhosis, the use of an alternative and safe method for evaluating the esophagus, especially in the setting of a screening strategy (*i.e.*, esophageal varices), is needed[5,6]. We found that for esophageal varices (independently of the size), E.G. Scan™ is an excellent option, with sensitivity, specificity and diagnostic accuracy of 95%, 97% and 97%, respectively. These results are similar to that reported by Choe *et al*[21], in a study where 100 cirrhotics were evaluated both by transnasal and standard endoscopy, showing that diagnostic accuracies of transnasal non sedated EGD for detecting esophageal varices, gastric varices and red color signs were 98%, 98% and 96%, respectively. Also, as in the Choe *et al*[21] study, we found that concordance rates on grading esophageal varices were excellent at 95% (κ = 0.91). These results are better than those reported by using endoscopy capsule for detection of esophageal varices[7-9].

With regards to erosive esophagitis diagnosed at upper endoscopy, E.G. Scan™ showed a sensitivity of 45% and specificity of 91%. These results are very similar to those reported by Sharma *et al*[8] in a study comparing ECE versus conventional endoscopy. In a recent study, Shariff *et al*[11] found that using a transnasal endoscope, a correct diagnosis of BE was obtained in 48 of 49 cases compared with the criterion standard, giving sensitivity and specificity of 98% and 100%, respectively. Although in our study the sensitivity was lower (67%), the specificity was 95% for the diagnosis of BE. In another study, Jobe *et al*[12] found that, in a cohort of 274 eligible adults scheduled for endoscopic screening for gastroesophageal reflux symptoms or surveillance of BE in a tertiary care center, the prevalence of BE was 26% using conventional endoscopy and 30% using unsedated small-caliber endoscopy (P = 0.503). In this study, the level of agreement between the two approaches was "moderate" (κ = 0.591). In our study, we found that agreement between E.G. Scan™ and EGD was 0.619. However, E.G. Scan™ misses about half of the cases of erosive esophagitis and one third of patients with Barrett's esophagus. It appears therefore that this version of E.G. Scan™ is not sufficiently sensitive for evaluation of acid reflux evaluation.

It is important to remark that, even although E.G. Scan™ has been developed for esophageal evaluation, in almost 40% of the cases we could reach the pylorus and the duodenum. We could do that because we asked patients to lie down in the left lateral position and then under direct visualization we advanced the probe. As shown in the figures, good quality images from the duodenum of patients with celiac disease and inflammatory duodenitis were obtained.

Regarding tolerability, we found that, as was reported by Chung *et al*[16], most of the patients experienced mild or no symptoms during the procedure and even if they reported mild symptoms, we could perform the evaluation in all cases. An unusual 100% success rate of nasal intubation with this device was found in our study, contrasting with other reports on transnasal endoscopy that present an average of 8% failure rate for nasal intubation due to anatomic nasal limitation or patient intolerance[22,23]. Although the probe shaft is 3 mm, its tip is 6 mm, a little larger than an ultra-slim endoscope, and we believe that the routine use of oxymetazoline hydrochloride, a selective alpha-1 agonist and partial alpha-2 agonist topical, influences such a high success rate for nasal intubation. Previous studies have shown that the use of oxymetazoline for pediatric nasendoscopy is effective,

safe and allows an ease of performance and cooperation of the patients[24]. Although we prepared the patient with an assurance of a successful nasal intubation, we did not use simethicone routinely, a compound that has been used in several studies to improve visibility[25].

Regarding costs, in our country the cost for the E.G. Scan™ device is 8000 USD and each probe costs 140 USD. However, costs can vary among countries and further cost-effectiveness studies are required. Although our study has the strength of a large, blinded evaluation and comparative study with conventional EGD, there are some limitations and technical issues that should be remarked on. The current version of the E.G. Scan™ does not have a channel for air insufflation or water ejection for wash or suction water and bubble air to improve the quality of images. Another major limitation is that it also does not have a biopsy channel to corroborate some conditions, such as BE or malignant lesions. Recently, the manufacturer has provided a new version of the E.G. Scan™ that has an insufflation channel and the bending angle of the tip probe is closed to 180°; thus retroversion at the stomach fundus can now be performed. Nowadays, slim endoscopes have much better quality than in the past with high-resolution images and digital chromoendoscopy and a complete EGD. E.G. Scan™ seems to be an alternative to ultra-slim endoscopes for transnasal examination. In the future, an ideal comparative trial will be performed between E.G. Scan™ and nasogastroscopes.

According to our results, we conclude that E.G. Scan ™ might represent an easy, safe and well tolerated procedure to investigate patients with suspected esophageal varices in the medical outpatient setting.

COMMENTS

Background

Esophagogastroduodenoscopy (EGD) is the most effective method to investigate disorders affecting the upper digestive tract. In particular, EGD is considered as the gold standard technique for the evaluation, diagnosis, screening and surveillance of esophageal diseases. Although EGD is widely used and available, the procedure is costly, may be unpleasant, and still has a small but potential risk of complications.

Research frontiers

Over the last years, a research hotspot has been the development of alternative methods to conventional EGD for the noninvasive or minimally invasive diagnosis of esophageal diseases, such as ultra-thin small caliber esophagoscopes.

Innovations and breakthroughs

Recently, a novel disposable transnasal esophagoscope, the E.G. Scan™ (IntroMedic Co. Ltd., Seoul, South Korea) has been developed. This transnasal esophagoscope does not require either a large endoscopy system or special equipment for disinfection; it is portable, disposable and well tolerated. In our study, we found that that E.G. Scan™ might represent an easy, safe and well tolerated first-line procedure to investigate patients with suspected esophageal varices in the medical outpatient setting.

Applications

Unsedated small-caliber transnasal esophagoscopy offers the possibility of efficient and accurate endoscopic assessment of the esophagus, with less cost and fewer risks compared with sedated upper endoscopy, and can be used as a method to screen for esophageal disease in a primary care population.

Terminology

Esophagogastroduodenoscopy: Esophagogastroduodenoscopy or panendoscopy is a diagnostic endoscopic procedure that visualizes the upper part of the gastrointestinal tract up to the duodenum. It is considered a minimally invasive procedure since it does not require an incision into one of the major body cavities and does not require any significant recovery after the procedure (unless sedation or anesthesia has been used). Esophagoscopy: Esophagoscopy is a procedure in which a flexible endoscope is inserted through the mouth, or more rarely through the nares, and into the esophagus. The endoscope uses a charge-coupled device to display magnified images on a video screen. The procedure allows visualization of the esophageal mucosa from the upper esophageal sphincter all the way to the esophageal gastric junction or esophagogastric junction.

Peer review

This is an interesting and well-designed prospective study that evaluated a new device called E.G Scan™ for endoscopic esophageal examination through the transnasal route compared to conventional EGD, with better results seen with the modified version of the scope. E.G. Scan™ seems to be an alternative to ultra-slim endoscopes for transnasal examination and the ideal comparative trial would have been between E.G. Scan™ and nasogastroscopes. Nowadays slim endoscopes have much better quality than in the past, with high-resolution images and digital chromoendoscopy, and they permit a complete EGD.

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BRIEF ARTICLE

Efficacy of SpyGlass™-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures

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Abstract

AIM: To evaluate the diagnostic yield (inflammatory activity) and efficiency (size of the biopsy specimen) of SpyGlass™-guided biopsy *vs* standard brush cytology in patients with and without primary sclerosing cholangitis (PSC).

METHODS: At the University Medical Center Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or long-standing PSC (19 patients) were screened for the study. All patients underwent a physical examination, lab analyses, and abdominal ultrasound. Thirty-one patients with non-PSC strictures or with PSC were scheduled to undergo endoscopic retrograde cholangiography (ERC) and subsequent per-oral cholangioscopy (POC). Standard ERC was initially performed, and any lesions or strictures were localized. POC was performed later during the same session. The Boston Scientific SpyGlass System™ (Natick, MA, United States) was used for choledochoscopy. The biliary tree was visualized, and suspected lesions or strictures were biopsied, followed by brush cytology of the same area. The study endpoints (for both techniques) were the degree of inflammation, tissue specimen size, and the patient populations (PSC *vs* non-PSC). Inflammatory changes were divided into three categories: none, low activity, and high activity. The specimen quantity was rated as low, moderate, or sufficient.

RESULTS: SpyGlass™ imaging and brush cytology with material retrieval were performed in 29 of 31 (93.5%) patients (23 of the 29 patients were male). The median patient age was 45 years (min, 20 years; max, 76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. No procedure-related complications were encountered. However, for both methods, tissues could only be retrieved from 29 patients. In cases of inflammation of the biliary tract, the diagnostic yield of the SpyGlass™-directed biopsies was greater than that using brush cytology. More tissue material was obtained for the biopsy method than for the brush cytology method (P = 0.021). The biopsies showed significantly more inflammatory characteristics and greater inflammatory activity compared to the cytological investigation (P = 0.014). The greater quantity of tissue samples proved useful for both PSC and non-PSC patients.

CONCLUSION: SpyGlass™ imaging can be recommended for proper inflammatory diagnosis in PSC patients. However, its value in diagnosing dysplasia was not addressed in this study and requires further investigation.

Key words: Cholangioscopy; Endoscopic retrograde cholangiopancreatography; Primary sclerosing cholangitis; Brush cytology; Biopsy

Core tip: Endoscopic retrograde cholangiography remains the gold standard method for diagnosing biliary tract diseases. However, choledochoscopy with the SpyGlass™ system enables direct visualization of the biliary tract. Furthermore, targeted biopsies can be performed. In our single-center study, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in primary sclerosing cholangitis (PSC) and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with significantly greater amounts of tissue for histological evaluation.

Rey JW, Hansen T, Dümcke S, Tresch A, Kramer K, Galle PR, Goetz M, Schuchmann M, Kiesslich R, Hoffman A. Efficacy of SpyGlass™-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures. *World J Gastrointest Endosc* 2014; 6(4): 137-143 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/137.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i4.137

INTRODUCTION

The precise diagnosis of biliary lesions and strictures is of crucial importance in patients with primary sclerosing cholangitis (PSC) or other biliary strictures because malignant tumors of the bile duct frequently have poor prognoses and high recurrence rates. Furthermore, the precise diagnosis of inflammatory activity influences medical and endoscopic treatments and might affect surveillance intervals.

The accurate assessment of bile duct stenosis (malignant *vs* inflammatory *vs* scar) is the ultimate goal of endoscopic retrograde cholangiopancreatography (ERCP) in patients with PSC. However, this differentiation remains challenging because endoscopic retrograde cholangiography (ERC) and other auxiliary fluoroscopy techniques do not permit the reliable diagnostic evaluation of biliary lesions[1,2]. Alternative diagnostic methods, such as endoscopic ultrasonography (EUS) with the use of miniprobes or probe-based endomicroscopy, are still of limited use[3].

Peroral cholangioscopy (POC) provides direct visualization of the biliary tree. This method also permits tissue sampling *via* targeted biopsies. The additional information provided by POC has been reported to change overall patient management and outcomes[4]. Furthermore, POC appears to be useful for clarifying filling defects during ERCP[5]. Recent data suggest that POC provides sufficient resolution and that in combination with biopsy, it can accurately diagnose biliary tract lesions[6]. POC is not a new process, as it has been used since the 1970s[7]. However, when first introduced, the procedure required two investigators, and the fiber-optic image quality was poor[8].

The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific and is known as the SpyGlass™ direct visualization system. The system enables a single investigator to perform cholangioscopy and targeted biopsies of bile duct abnormalities[9]. After the SpyGlass™ direct visualization system was introduced, its clinical application was reported in several publications. The main aspects addressed in these studies were the accessibility, direct view, and characterization of abnormal biliary lesions[10,11]. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%)[12].

However, ERC remains the gold standard for diagnosing biliary lesions in PSC[13]. Although brush cytology is the preferred investigation method for strictures and PSC-associated lesions, the poor sensitivity has been reported to be a major problem. Cytology achieves fairly good specificity, but its sensitivity is poor (approximately 50%)[14-19]. Cholangioscopy-guided biopsy appears to have the potential to overcome the problems associated with inadequate tissue sampling.

Thus, the aim of the present study was to evaluate the diagnostic yield (inflammatory activity) and efficiency (the biopsy specimen size for histological evaluation) of SpyGlass™-guided biopsy versus standard brush cytology.

MATERIALS AND METHODS

Patient recruitment

From January 2009 to February 2011 at the University Medical Center of Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or longstanding PSC (19 patients) were screened for the study. Thirty-one patients were finally included in the study after providing informed consent. All patients underwent a physical examination, lab analyses (Table 1), and abdominal ultrasound prior to ERCP and POC.

Endoscopic system and technique

The Boston Scientific SpyGlass™ and the Boston Scientific SpyScope™ were used for choledoscopy. The choledochoscope was advanced through a standard therapeutic duodenoscope (Pentax ED-3480T, Pentax, Hamburg). The choledochoscope (Boston Scientific™) was passed through the working channel of the "mother" scope (Pentax ED-3480T duodenoscope). All procedures were

Table 1 Patient characteristics

	All patients	PSC	Non-PSC	*P* value
Patients (*n*)	29	19	10	-
Age	(48.9 ± 16.7)	(42.1 ± 13.9)	(61.9 ± 13.9)	0.00172
ALT	(100.2 ± 129.1)	(69.5 ± 41.1)	(155.4 ± 203.9)	0.21921
AST	(74.5 ± 69.0)	(63.7 ± 104.7)	(93.9 ± 107.7)	0.39791
Gamma GT	(411.4 ± 470.7)	(314.7 ± 288.4)	(585.2 ± 674.8)	0.25288
AP	(310.4 ± 212.6)	(285.0 ± 177.3)	(356.0 ± 269.6)	0.46748
Bilirubin	(3.0 ± 4.9)	(2.9 ± 5.0)	(3.3 ± 5.1)	0.83431
CRP	(20.8 ± 32.0)	(15.4 ± 25.9)	(30.3 ± 40.5)	0.31297
Leukocytes	(8.1 ± 3.1)	(8.2 ± 3.3)	(7.7 ± 2.6)	0.66937

PSC: Primary sclerosing cholangitis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein.

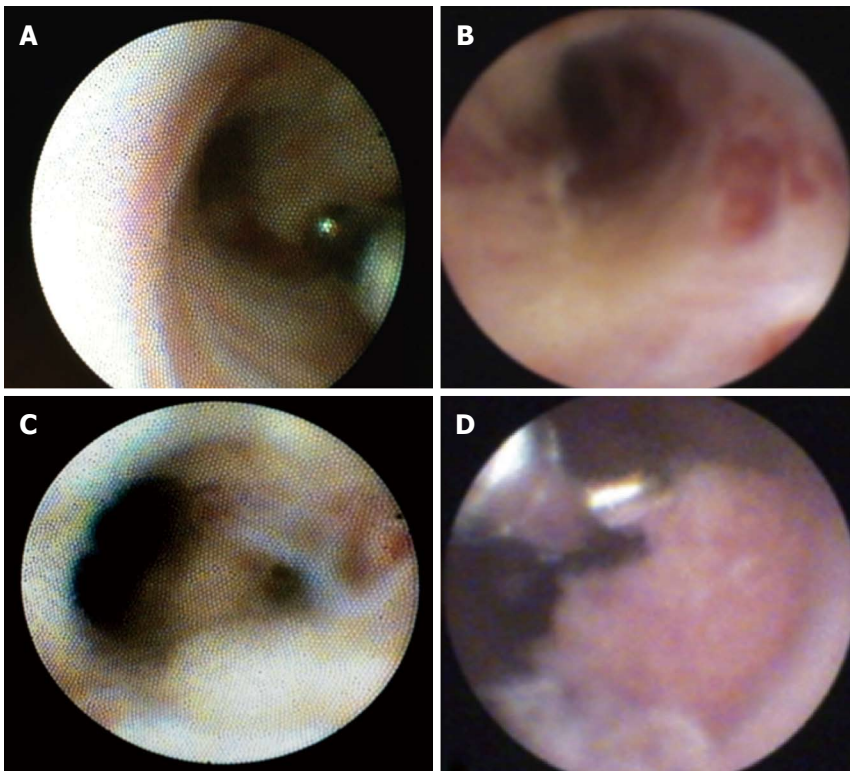

Figure 1 SpyGlass™ visualization of the bile duct. A: A normal bile duct; B: Chronic inflammation, with scars; C: Active inflammation, with mucus fibrin; D: Targeted biopsy of a lesion.

performed using Propofol (1% Disoprivan, AstraZeneca, Switzerland) as sedation.

Before POC, a standard retrograde cholangiogram with biliary sphincterotomy was performed to localize the strictures and to facilitate ductal access and therapy. The choledochoscope was introduced into the bile duct through the guidewire *via* the working channel. For patients in whom the wire could not be advanced beyond a lesion or stenosis, the guidewire was advanced to the stricture under direct visualization of the bile duct whenever possible.

ERCP, POC, and tissue sampling techniques

Standard ERC was initially performed, and any lesions or strictures were localized. Subsequently, POC was performed during the same session. The biliary tree was inspected, and suspicious lesions or strictures were biopsied; at least two or three biopsies per lesion or stricture were taken for histological examination (Figure 1). In addition, brush cytology of the same area was performed with a Cook medical Double Lumen Biliary Brush™ (Cytology). A single pathologist who specialized in biliary pathology graded the biopsy specimens and the brush cytology (T.H.) in a standardized manner. The inflammatory changes were divided into 4 categories (none, low, moderate, high) according to the number of leukocytes. For the biopsies, 5 high-power fields (HPFs, 0.309 mm^2) were observed, and the leukocytes were semiquantitatively analyzed as follows: no activity, < 10 leukocytes/HPF; low activity < 100 leukocytes/HPF; moderate activity > 100 leukocytes/HPF; and high activity > 150 leukocytes/HPF. In the case of the cytological specimens,

Table 2 Quantity of material

		Brush			Total
		Small	Moderate	Sufficient	
Biopsy	Small	3	4	0	7
	Moderate	6	4	2	12
	Sufficient	9	1	0	10
Total		18	9	2	29

Quantity of material by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.021.

Table 3 Inflammatory activity

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	11	0	0	11
	Moderate	0	8	0	0	8
	High	1	6	0	2	9
Total		1	26	0	2	29

Signs of inflammation by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.014.

semiquantitative evaluation revealed the following activity levels: none, < 5 leukocytes/HPF; low, < 50 leukocytes/HPF; and high, > 50 leukocytes/HPF. The quantity of specimens was rated as low, moderate, or sufficient, according to the cell number in an HPF (0.306 mm^2); in the case of cytology, the quantities were as follows: low, < 10 cells/HPF; moderate, < 20 cells/HPF; and sufficient, > 50 cells/HPF). In biopsy specimens, either the number of specimens (low, one tissue fragment; moderate, at least two tissue fragments; sufficient, at least three tissue fragments) or the number of mucosal folds/villi was encountered (low, one villus; moderate, at least two villi; sufficient, at least three villi).

Ethical considerations

The ethics committee of Rheinland-Pfalz, Germany, approved this study (No. 837.432.07 (5967)).

Statistical analysis

Practical limitations allowed us to collect material from 31 patients; 2 samples did not meet our quality criteria. The material collection proved to be sufficient to detect the differences between the two groups. Statistical analysis was performed using the R statistical language. Bowker's test was used to reject the null hypothesis of symmetry in contingency tables (Tables 2 and 3):

$$\sum_{i<j} \frac{(n_{ij} - n_{ji})^2}{n_{ij} + n_{ji}}$$

, where B is χ^2 distributed with $[n(n-1)]/2$ degrees of freedom.

All reported *P* values are the result of a data exploration process.

RESULTS

All 31 patients underwent brush cytology and biopsy. No procedure-related complications were encountered. However, for both methods, tissues could be retrieved from only 29 patients. In one patient, SpyGlass™ failed to obtain any tissue material; in another patient, no cytological specimens could be obtained using brush cytology.

The patient and laboratory characteristics are summarized in Table 1. Twenty-three of the 29 patients were male, and the median patient age was 45 years (range, 20-76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. The patient characteristics did not significantly differ between the two groups. Four patients had a suspicion of malignant strictures during endoscopy that was not confirmed by histologic results.

The biopsy method revealed significantly more tissue material ($P = 0.021$) than the brush method (Table 2, Figure 2). In 10 patients, the number of biopsy specimens was sufficient; by contrast, only 2 patients demonstrated sufficient numbers of specimens by brush cytology. In 27 patients, no or little inflammatory activity was detected using the brush method, compared to 12 patients using the biopsy method. Using SpyGlass™-directed biopsy, a greater degree of inflammatory activity (classified as moderate or high) was observed in 17 of 29 (58.62%) patients ($P = 0.014$) (Table 3). Brush cytology failed to reveal any significant signs of inflammation because of the paucity of material. A common characteristic of the two techniques was that a greater quantity of test material predicted stronger signs of inflammation. The subgroup analysis between the PSC and non-PSC patients did not reveal any significant differences in the assessment of inflammatory activity with regard to the biopsy or brush method, respectively (Tables 4, 5). Neither brush cytology nor biopsy detected any malignant strictures or dysplasia in the patients.

The brush method demonstrated a positive correlation between the amount of test material and the characteristics of inflammation. This method typically produced little study material and revealed only a few features of inflammation. SpyGlass™-directed biopsy showed moderate or high levels of inflammation in 17 of 29 cases.

A significantly greater quantity of material was obtained with the biopsy-directed procedure. Brush cytology showed adequate signs of inflammation in two cases (Table 2). We observed no differences in the outcomes of the patients with or without PSC. Furthermore, no significant difference was noted in the patients with elevated laboratory parameters of inflammation with regard to the histopathological signs of inflammation.

DISCUSSION

SpyGlass™ is a single-operator system that allows direct visualization of the biliary and pancreatic tracts[9,20]. SpyGlass™ provides significantly greater sensitivity to clarify biliary strictures compared to ERCP[12,21,22]. The largest study in the literature (comprising nearly 300 patients)

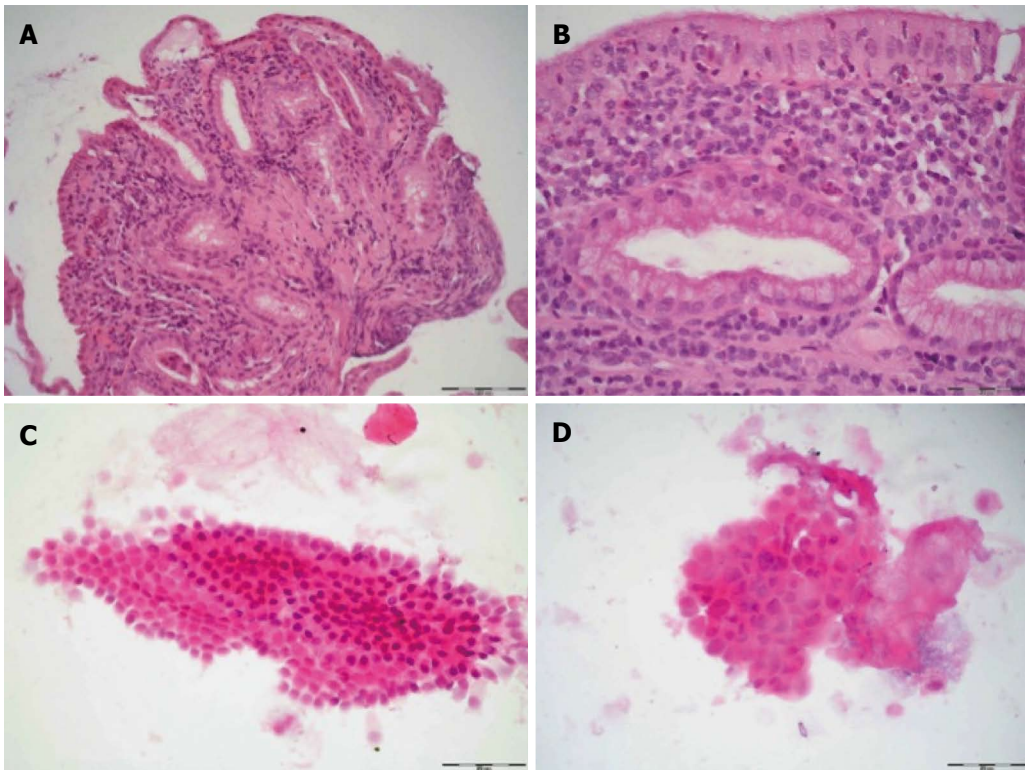

Figure 2 Comparison of biopsy and brush cytology. Histological examination of the biopsy (A, B) shows parts of the bile duct wall with regularly shaped epithelium (original magnification, × 100 A, × 400 B). A detailed view in B confirms marked inflammation with numerous lymphocytes and neutrophilic granulocytes infiltrating the bile duct mucosa. Cytological analysis of the same patient was in the upper figures (original magnification C, D), demonstrating regular epithelial cells and few leukocytes.

showed that SpyGlass™ could visualize 96% of all strictures and that 88% of the identified strictures or lesions could be successful biopsied[23]. Other studies reported a higher diagnostic value of SpyGlass™-guided biopsy compared to brush cytology[24-26]. However, to date, the diagnostic yield for PSC has not been clarified. Thus, we investigated the diagnostic value of SpyGlass™-directed biopsy versus brush cytology in patients with or without PSC. Furthermore, we evaluated whether the biopsy or brush cytology characteristics differed between PSC and non-PSC patients. We clearly demonstrated that SpyGlass™-guided biopsy obtained greater quantities of tissue specimens and provided a more accurate diagnosis of inflammatory changes. This result is important because the degree of inflammation might alter the medical treatment or refine the surveillance of PSC patients.

Our study focused on the amount of tissue obtained and the presence of inflammatory changes. Although malignant changes were suspected in four of our patients during endoscopy, the specimens could not confirm dysplasia or carcinoma. However, malignancies have been identified using SpyGlass™, with a reported accuracy of 77% in patients with suspected cholangiocarcinoma[4,25-28]. Our study could not clarify whether SpyGlass™ is beneficial in identifying PSC-associated dysplasia.

In our study, biopsy specimens were obtained using SpyGlass™ in 28 of 29 cases (96.5%). This percentage is greater than that previously reported[11], which might be because we performed at least 2-3 passes of the biopsy forceps (Spybite™) at the area of interest.

Brush cytology often failed to reveal signs of inflammation because of the paucity of material. The most important result of our study was that tissue acquired by directed biopsy was associated with greater signs of inflammation that allowed a more precise diagnosis because SpyGlass™-directed biopsy acquired a greater amount of sample, at quantities adequate for analysis. Pathological examination improved the diagnosis of inflammation by the amount of specimens. This result occurred significantly more often in the biopsied specimens. These data are relevant with regard to patients with unknown biliary strictures and concur with another study in which the initial working diagnosis was modified after a SpyGlass™ investigation in 68.9% of patients with biliary strictures[29]. Specific risk populations (*e.g.*, patients with PSC or prolonged chronic inflammation of the bile duct) are subject to an increased risk of cancer[30,31]. As POC provides direct information about the bile duct, it may serve as an important and informative extension of ERC[22].

Note that there were no complications related to the SpyGlass™ examination. In addition to the expected result of improved detection of inflammation in SpyGlass™-directed biopsy, we also demonstrated that the method was easy and safe, as previously reported[32].

The present study had some limitations. First, we had to perform brush cytology after biopsy, and the influence of the quantity of the brush cytology specimens remains unknown. Second, this study was performed at a single

Table 4 Inflammatory activity in primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	0	0	0	0
	Low	0	6	0	0	6
	Moderate	0	4	0	0	4
	High	1	6	0	2	9
Total		1	16	0	2	19

Signs of inflammation (by method) for the patients diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.088.

Table 5 Inflammatory activity in non-primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	5	0	0	5
	Moderate	0	4	0	0	4
	High	0	0	0	0	0
Total		0	10	0	0	10

Signs of inflammation (by method) for the patients who were not diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.544.

center with a limited number of patients. Third, a single pathologist performed all the histopathological examinations.

In conclusion, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in PSC and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with the greater amount of tissue specimens obtained from the SpyGlass™-directed biopsy. A total of 2-3 biopsies must be obtained from suspicious areas in the biliary tract. Further studies are needed to fully clarify the benefit of the better inflammatory diagnosis in PSC and to investigate the potential of SpyGlass™ in diagnosing PSC-associated dysplasia.

COMMENTS

Background

Patients with primary sclerosing cholangitis (PSC) suffer from chronic and relapsing inflammation of the biliary tract. Endoscopic retrograde cholangiopancreatography is recommended procedure to stage the disease and to clarify inflammatory strictures. Spyglass™ as a single operator cholangioscopy system provides direct visualization of the biliary tract with the possibility of direct biopsies.

Research frontiers

Cholangioscopy is basically not a new process. It has been introduced since the 1970´s as a so-called mother-baby endoscopy technique, in which a thin choledochoscope (baby-scope) was pushed through the instrumentation channel of the duodenoscope (mother-scope) during the endoscopic retrograde cholangiography (ERC). The procedure required two investigators and the quality of the fiber-optic images was poor. The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific, and is known as the SpyGlass™ direct visualization system.

Innovations and breakthroughs

Precise diagnosis of biliary lesions and strictures is still difficult but of crucial importance for the patients. However, neither ERC nor other auxiliary fluoroscopy-techniques permit reliable diagnostic evaluation of biliary lesions. The gold standard for the diagnosis of biliary lesions, especially in PSC, is still ERC. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%) and biliary strictures could be significant better characterized. Furthermore the SpyGlass™ system allows optical guided biopsy sampling with definite histologic diagnosis and high accuracy.

Applications

This study indicates that the diagnostic yield of SpyGlass™-directed biopsies for inflammatory changes in PSC and non-PSC patients is significantly higher than that of brush cytology. The better diagnostic yield is strongly correlated with the larger amount of tissue specimens, which can be obtained with SpyGlass™ directed biopsies.

Terminology

The SpyGlass System was developed to overcome the limitations of the so called traditional cholangioscopy. Integrated irrigation channels and a 1.2 mm diameter therapeutic channel make for the first time optical guided biopsies and therapeutic stone management possible. Thus, this system enables for a single investigator during ongoing ERC to perform targeted biopsy of bile duct lesions and to perform laser therapy of complicated bile duct stones.

Peer review

This study is well conducted even if only a few patients were included. In this study the advantages of direct cholangioscopy with the possibility of using a single operator cholangioscopy and with the possibility of direct biopsies are well described. The results showing significant advantages of biopsy versus brush cytology in grading inflammation and non-inflammatory changes in the bile duct.

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CASE REPORT

Rare presentation of primary (AL) amyloidosis as gastrointestinal hemorrhage without systemic involvement

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Abstract

We are reporting a rare case of a patient with primary (AL) amyloidosis presenting with an acute non-variceal upper gastrointestinal hemorrhage in the absence of other systemic involvement. The case report involves a 58-year-old woman with significant cardiac history and hereditary blood disorder who came in complaining of abdominal pain and coffee-ground emesis for two days. Computed tomography (CT) scan of the abdomen and pelvis with contrast revealed segmental wall thickening of the proximal jejunum with hyperdense, heterogenous luminal content. Similar findings were evident in the left lower small bowel region, suspicious for small bowel hematoma and the possibility of intraluminal clots. Esophagogastroduodenoscopy performed post resuscitation showed punctate, erythematous lesions throughout the stomach as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Despite initial treatment for immunostain-positive focal cytomegalovirus gastritis, follow-up esophagogastroduodenoscopy after two months continued to demonstrate friable and irregular duodenal mucosa hinting at a different underlying etiology. Pathology reports from analyses of biopsy samples highlighted infiltration and expansion of the lamina propria and submucosa. Subsequent staining with congo red/crystal violet and appropriate subtyping established the diagnosis of AL (kappa)-type amyloidosis. The significance of this case lies in the fact that our patient did not have the typically seen diagnostic systemic involvements-namely of heart and kidneys-usually seen in primary (AL) amyloidosis patients. It was the persistent endoscopic findings and biopsy results which gave clues to the physicians regarding the possibility of an abnormal protein-deposition entity.

Key words: Primary amyloidosis; AL amyloidosis; Gastrointestinal hemorrhage; Endoscopic finding; Endoscopic biopsy; Upper gastrointestinal bleeding; Amyloid deposition; Gastric/intestinal mucosa; Mucosal inflammation

Core tip: This case report of a 58-year-old African-American woman with coffee-ground emesis highlights a rare instance where AL (kappa)-type amyloidosis presents as gastrointestinal hemorrhage in the absence of clinical disease elsewhere in the body. Esophagogastroduodenoscopy initially revealed punctate, erythematous lesions throughout the stomach as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Patient was treated for cytomegalovirus gastritis based on biopsy results. However, repeat enteroscopy continued to demonstrate friable and irregular duodenal mucosa with pathology highlighting infiltration and expansion of the lamina propria and submucosa. Appropriate staining and sub-

typing established AL (kappa)-type amyloidosis.

Ali MF, Patel A, Muller S, Friedel D. Rare presentation of primary (AL) amyloidosis as gastrointestinal hemorrhage without systemic involvement. *World J Gastrointest Endosc* 2014; 6(4): 144-147 Available from: URL: http://www.wjgnet.com/1948-5190/full/v6/i4/144.htm DOI: http://dx.doi.org/10.4253/wjge.v6.i4.144

INTRODUCTION

Primary (AL) amyloidosis is an infrequent disorder and the exact incidence is unknown. In the United States, there is roughly 6 to 10 cases per million person-years[1]. The median age at diagnosis is 64 years. There is a male predominance with men accounting for 65% to 70% of patients[2].

Amyloidosis involves the extracellular deposition of protein fibrils. Primary (AL) amyloidosis, as diagnosed in our patient, is associated with monoclonal light chains in serum and or urine. The kidneys and heart are the most commonly involved organs. However, the nervous system, lungs, liver, soft tissue and the gastrointestinal (GI) tract can be involved as well[3].

The occurrence of clinically evident gastrointestinal involvement depends on the type of amyloidosis. While as many as 60% of patients with reactive amyloidosis display gastrointestinal disease, it appears far less common in AL amyloidosis.

CASE REPORT

A 58-year-old African-American woman with history of sickle cell disease, atrial fibrillation, Wolff-Parkinson-White syndrome and AICD presented with epigastric pain, coffee-ground emesis for 2 d. Patient denied nausea, early satiety, constipation, or dysphasia. She was found to have a hemoglobin level of 4.5 g/dL and was positively orthostatic, consequently requiring fresh frozen plasma (FFP) and multiple units of packed red blood cells (RBCs). The patient was started on continuous IV proton pump inhibitor (PPI) and admitted to ICU for close monitoring.

Computed tomography (CT) abdomen/pelvis with contrast showed segmental wall thickening of the proximal jejunum with hyperdense, heterogenous luminal content. Similar findings were evident in the left lower small bowel region, raising suspicion for small bowel hematoma with the possibility of intraluminal clots. Esophagogastroduodenoscopy post-resuscitation revealed punctate, erythematous lesions throughout the stomach (including the cardia) as well as regions of small bowel mucosa that appeared scalloped, ulcerated, and hemorrhaged on contact. Biopsies suggested marked acute duodenitis with blood, fibrin, and acute inflammatory exudates, indicative of the bleeding site (Figure 1B). Immunostains of these

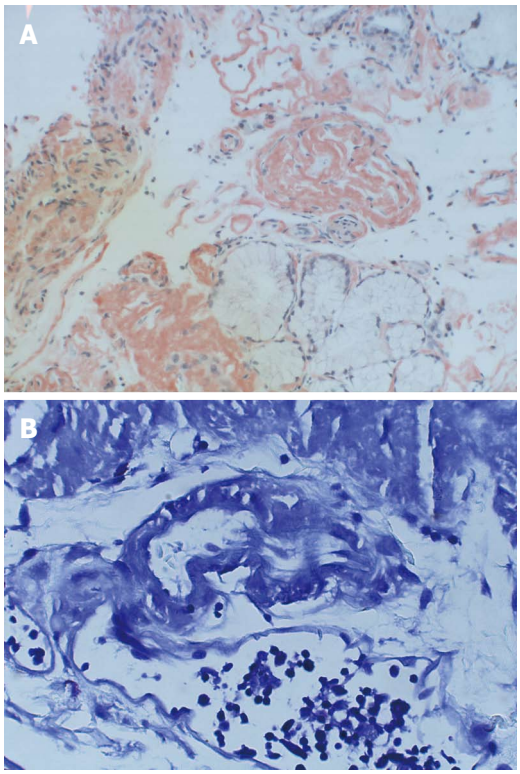

Figure 1 Small bowel biopsies with multiple immunostains confirming amyloid deposition. A: Duodenal Biopsy; Congo Red (× 20); Infiltration and expansion of the lamina propria and submucosa by amyloid deposition staining positive for Congo-Red; B: Small Bowel Biopsy; Crystal Violet (× 40); Marked acute duodenitis with blood, fibrin, and acute inflammatory exudates, suggestive of bleeding site. Crystal Violet stain positive for amyloid.

samples indicating focally active gastritis were positive for cytomegalovirus (CMV). Treatment with Valganciclovir (900 mg every 12 h) for 21 d was initiated.

A repeat enteroscopy 2 mo later to assess for healing, continued to demonstrate friable and irregular duodenal mucosa (Figure 2). There was oozing from areas of scope contact and biopsy sites. Argon plasma coagulation was used to achieve hemostasis. Pathology underlined infiltration and expansion of the lamina propria and submucosa (Figure 1A) in addition to eosinophilic deposition around blood vessels (Figure 3). Immunostain was negative for CMV. Congo Red/Crystal Violet staining however, was positive, and appropriate subtyping subsequently established AL (kappa)-type amyloidosis.

DISCUSSION

The clinical diagnosis of gastrointestinal amyloidosis can be challenging in patients in whom the presence of this disease entity has not yet been established. Rarely does AL-amyloid present in the gastrointestinal tract as acute GI hemorrhage without other systemic symptoms[4]. Cardiac involvement, seen in 90% of the cases, is marked by congestive heart failure (CHF) and arrhythmias due to restrictive cardiomyopathy[5]. Diastolic dysfunction contributing to heart failure is apparent on echocardiography. Our patient had normal left ventricular systolic function

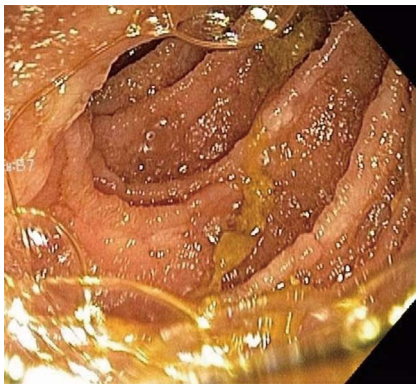

Figure 2 Second segment of the duodenum demonstrating notched mucosal appearance.

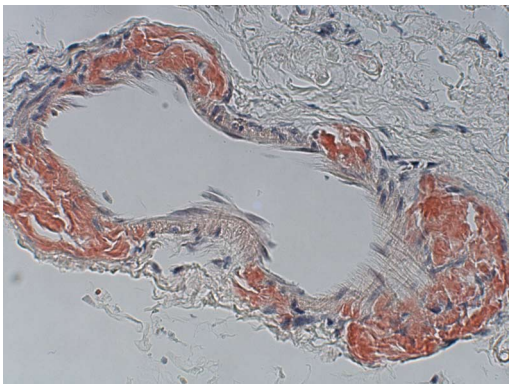

Figure 3 Colon Biopsy; Congo Red (× 40). Fragments of colonic mucosa and separate fragments of submucosa with eosinophilic material deposited around blood vessels, consistent with amyloid deposition. Congo Red stain positive.

and although she had abnormal left ventricular diastolic function, her E/A ratio was 1.3. The E/A ratio is usually greater than 2.0 in the restrictive cardiomyopathy associated with amyloidosis[6]. Additionally, the patient did not display any clinical signs of heart failure (*e.g.*, lower extremity swelling of jugular venous distention). Renal insufficiency and/or nephrotic syndrome was also lacking in our patient.

Gastrointestinal manifestations appear to be less common in AL amyloidosis, with biopsy diagnosed disease and clinically apparent disease occurring in only 8% and 1% respectively of 769 patients in a retrospective review[7]. Despite the infrequency of gastrointestinal manifestations, the small intestine is the site of greatest deposition when there is involvement. Duodenal amyloidosis results in scalloped edges, duodenitis, ulcers, masses, hypotonia, and dilatation[8-10]. Endoscopic findings commonly include a fine granular appearance, polyps, erosions, ulcerations, and mucosal friability[11]. Clinical signs and symptoms may include hemorrhage, obstruction, and infarction amongst others.

Bleeding occurs as a presenting symptom in 25%-45% of patients with amyloidosis and may be caused by ischemia or infarction, by ulceration or an infiltrated lesion, or from generalized oozing without a particular source[12]. Endoscopy shows diffuse involvement, such as esophagitis and gastritis, more often than discrete lesions, as observed in our patient.

COMMENTS

Case characteristics

A 58-year-old African-American woman with history of sickle cell disease, atrial fibrillation, Wolff-Parkinson-White syndrome and AICD presented with epigastric pain, coffee-ground emesis for 2 d.

Clinical diagnosis

Tenderness to palpation in the epigastric region on abdominal exam.

Differential diagnosis

Multiple myeloma, chronic lymphocytic leukemia, Amyloidosis, Gastritis.

Laboratory diagnosis

Hemoglobin 4.5 g/dL; Hematocrit 13.4%; INR 2.15.

Imaging diagnosis

CT scan of the abdomen and pelvis showed marked segmental wall thickening of the proximal jejunum and parts of the small bowel, with hyperdense, heterogenous walls/luminal content.

Pathological diagnosis

Small bowel biopsy (duodenum) showed infiltration and expansion of the lamina propria and submucosa by Congo-red and crystal violet-positive amyloid.

Treatment

Symptom control, *e.g.*, blood transfusion/fluid resuscitation, monitoring vitals.

Related reports

AL-amyloid rarely presents in the gastrointestinal tract as acute GI hemorrhage without other systemic symptoms.

Term explanation

The E/A ratio is a marker of the function of the left ventricle of the heart and is calculated on echocardiography with abnormalities indicative of diastolic dysfunction.

Experiences and lessons

This case report highlights the importance of endoscopic findings and biopsy revelations in making a diagnosis of amyloidosis in patients without other systemic manifestations.

Peer review

The paper is well written and reports an interesting case.

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Conference paper

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Electronic journal (list all authors)

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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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