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ORIGINAL ARTICLE

Retrospective Study

Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a United Kingdom Caucasian population

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Author contributions: Ang Y designed the study, supervised the project, obtained the data and wrote the manuscript; Sooltangos A coordinated the study, obtained and analysed the data, and wrote the manuscript; McGrath S reviewed all pathology reports and contributed to data analysis; George R and Ang Y performed the ESD and analysed the data; Vickers J, Senapati S and Akhtar K performed surgery and analysed the data.

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Abstract

AIM

To investigate the efficacy of endoscopic submucosal dissection (ESD) at diagnosing and treating superficial neoplastic lesions of the stomach in a United Kingdom Caucasian population.

METHODS

Data of patients treated with or considered for ESD at

a tertiary referral center in the United Kingdom were retrieved for a period of 2 years (May 2015 to June 2017) from the electronic patient records of the hospital. Only Caucasian patients were included. Primary outcomes were curative resection (CR) and were defined as ESD resections with clear horizontal and vertical margin and an absence of lympho-vascular invasion, poor differentiation and submucosal involvement on histological evaluation of the resected specimen. Secondary end-points were reversal of dysplasia at 12 mo endoscopic follow-up and/or at the latest follow up. Change in histological diagnosis pre and post ESD was also analysed.

RESULTS

Twenty-four patients were initially identified with intention to treat. 19 patients were eligible after mapping gastroscopy and ESD was attempted on a total of 25 ESD lesions, 4 of which failed and had to be aborted mid-procedure. Out of 21 ESD performed, en-bloc resection was achieved in 71.4% of cases. Resection was considered complete on endoscopy in 90.5% of cases compared to only 38.1% on histology. A total of 6 resections were considered curative (28%), 5 non-curative (24%) and 10 indefinite for CR or non-CR (24%). ESD changed the histological diagnosis in 66.6% of cases post ESD. Endoscopic follow-up in the "indefinite" group and CR group showed that 50% and 80% of patients were clear of dysplasia at the latest follow-up respectively; 2 cases of recurrence were observed in the "indefinite" group. Survival rate for the entire cohort was 91.7%.

CONCLUSION

This study provides early evidence for the efficacy of ESD as a therapeutic and diagnostic intervention in Caucasian populations and supports its application in the United Kingdom.

Key words: Endoscopic resection; Endoscopic submucosal dissection; Endoscopic mucosal resection; Dysplasia; Early gastric cancer; United Kingdom

Core tip: Endoscopic submucosal dissection (ESD) is a minimally invasive technique used to diagnose or treat early neoplastic lesions of the gastrointestinal tract. Imported from Far East countries, where it is extensively used, this intervention has proven to be highly effective in carefully selected patients and to constitute a viable alternative to radical surgery. ESD is relatively new in the West and local evidence to support its use in the United Kingdom lacking. This retrospective study provides early evidence in favour of the use of ESD in the United Kingdom.

Sooltangos A, Davenport M, McGrath S, Vickers J, Senapati S, Akhtar K, George R, Ang Y. Gastric endoscopic submucosal dissection as a treatment for early neoplasia and for accurate staging of early cancers in a United Kingdom Caucasian population. *World J Gastrointest Endosc* 2017; 9(12): 561-570 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i12/561.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i12.561

INTRODUCTION

Endoscopic resection (ER) is a minimally invasive technique aimed at staging or curing dysplastic lesions and intramucosal cancers of the gastrointestinal tract. ER includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), their respective application mainly depending on the size of the tumour[1]. EMR was the first endoscopic treatment proven to be as effective as gastrectomy at managing early gastric cancers, with curative rates as high as 85%[1]. However, in lesions larger than 20mm, ESD is preferred as it can achieve higher rates of en-bloc resections and consequently lower recurrence rates[1-7]. *En-bloc* resections almost constitute a prerequisite for accurate histological evaluation of the resected specimen.

ER is also considered the only definitive method of excluding invasion in otherwise precancerous lesions, where time and again, endoscopic biopsies and endoluminal ultrasound have proven inadequate[2,8,9]. ER can change the diagnosis in up to 40% of cases, more commonly resulting in an upstaging[10-12]. It provides vital information about the depth of invasion of the tumour and as the latter constitutes the strongest predictor of lymph node metastasis[13,14], it is used to guide subsequent management decisions, in particular the indication for surgery. When compared to surgery, ESD appears to have comparable oncologic outcomes with the advantage of shorter operation times, shorter hospital stays and lower complication rates[15].

Most evidence for the efficacy and safety of ESD comes from Eastern countries, where ESD has been shown to achieve curative resection (CR) rates as high as 97% in lesions that meet the Japanese Gastric Cancer Association (JGCA) guidelines[16-18]. Despite being a technically challenging procedure and carrying a high risk of adverse events in inexperienced hands[19], ESD is gradually gaining popularity in Western countries, partly facilitated by technological advancements[20]. However, evidence for ESD is still scarce in Western populations. One of the few studies carried out in Germany showed promising results with a high rate of en-bloc resections and remarkably low recurrence rates of 1.5%[21]. In the United Kingdom, the JGCA criteria guidelines are used to select lesions amenable to ESD. However, since the outcomes of ESD are heavily dependent on the level of skills of the endoscopist, more local studies are crucial[22,23]. The National Institute of Health and Care Excellence in the United Kingdom only take into account United Kingdom studies when formulating local clinical guidelines. No studies have considered the efficacy of gastric ESD in a United Kingdom Caucasian population

up to this date.

MATERIALS AND METHODS

This retrospective study is part of our service development and audit and aims to investigate the efficacy of ESD at treating early neoplastic lesions of the stomach in a Caucasian population at a tertiary referral centre in the United Kingdom and secondly, its application for staging early cancers.

Inclusion criteria: Data was obtained for a period of 2 years from May 2015 to June 2017. Only Caucasian patients with gastric cancers staged at or below T1a N0M0 on the basis of computed tomography (CT) scans (or Positron Emission Tomography-Computed Tomography (PET-CT) in a few cases) and Endoscopic Ultrasound (EUS) were included in this study.

Exclusion criteria: Patients with gastric cancers staged at T1bN0M0 or above were excluded from the study on the basis of CT scans (or PET-CT scans in a few cases) and EUS .

Mapping oesophagogastroduodenoscopy (mapping OGD, a pre-ESD check to evaluate if the case is suitable for ESD) was used to assess the macroscopic appearance of the lesions, the position and size, the presence of ulceration, any field changes and importantly whether the lesions were liftable. The degree of lift of each lesion was graded according to the Kato classification where Kato 1 denotes lifting without any resistance, Kato 2 lifting with some resistance and Kato 3 no lifting[24]. Endoscopic imaging enhancements used included White Light Imaging, Olympus Narrow Band Imaging (NBI) or Fuji Fluorescent Intelligent Chromoendoscopy, indigo carmine spray and acetic acid spray. Biopsies were taken prior to any intervention to assess or re-assess the type of neoplasia present and the degree of differentiation. Poor differentiation and non-lifting sign (Kato 3) precluded ESD except in one patient whose co-morbidities notably liver cirrhosis Child's Grade A made him unfit for surgery. Endoscopy reports, histology reports and multidisciplinary team (MDT) meeting letters were retrieved from the electronic patient record of the hospital. The information about each patient's demographic data, pre-ESD endoscopic assessment, index procedure, follow-up endoscopy, surgery and outcome at the latest follow up were recorded. Microsoft Excel has been used to record all data and for all statistical analyses.

Olympus Double Channel Double-Headed Scope or Fuji Dual Channel Endoscope were used in all procedures and the procedures were jointly performed by two experienced interventional gastroenterologists. The ESD procedure was carried out in theatre (operating room) with the patient under general anaesthesia. The patient was intubated with the assistance of an anaesthetist and endoscopy performed using carbon dioxide gas only. The ESD equipment used for dissection included Olympus ITknife2 Electrosurgical Knife (KD-611L), Olympus ITknife nano Electrosurgical Knife (KD-612L/U), Fujifilm Flush Knife, Fujifilm Clutch Clutter and ERBE Hybrid O Knife. A soft transparent hood (D-201-13404; Olympus, Tokyo, Japan) was attached to the tip of the endoscope to obtain good endoscopic views of the submucosal layer. In some cases, additional image enhancing techniques (as outlined above) had to be used. This was done through a 2-channel scope equipped with multibending and water jet functions attached to the tip of the endoscope. The lesions were lifted with EMR solution and marking dots were placed using argon on the normal mucosa at approximately 5 mm from the tumour margin to provide safety margins. EMR solution (consisting of a small amount of indigo carmine and 0.1% lidocaine) was then injected into the submucosal layer and a mucosal incision made outside the marking dots. In case of poor mucosal elevation due to ulceration of the lesion or extensive fibrosis of the submucosal layer, hyaluronic acid solution was added to the injection solution to achieve better lift. After mucosal incision, dissection of the submucosal layer was performed, thus achieving *en bloc* resection.

Each patient was given oral Omeprazole 40 mg, twice daily for at least 3 mo (or another equivalent proton pump inhibitor) after the procedure.

The resected specimen was cut into 4-mm-thick slices after formalin fixation. The histological type, size, depth of invasion, horizontal and vertical margins (HM and VM respectively), and lympho-vascular invasion were evaluated in each slice according to the JGCA Japanese Classification of Gastric Carcinoma criteria. To reconcile and allow for the efficacy of ESD to be more accurately investigated in Western populations, a more systematic approach to reporting histological findings such as the Vienna classification was also used[25]. The measure of efficacy in this study is CR. A resection is considered curative if it achieves clear vertical and horizontal margins and if histological evaluation of the resected specimen shows neither poor differentiation, nor lympho-vascular invasion nor submucosal involvement[3]. An ESD resection is coded as non-CR if it fails to meet all aforementioned criteria and as "indefinite" if data is inadequate to confirm either CR or non-CR. All resected lesions were coded as "complete resection on endoscopy" unless otherwise specified; a resection was considered to be "complete resection on histology" if the VM and the horizontal margin (HM) were clear on histology. The position of lesion was coded as Upper stomach if it was found in the cardia or fundus, as Mid stomach if in the body and as Lower stomach if in the antrum, pylorus or incisura. The age of the patient was at the time of the index procedure.

The secondary end-point was complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at the latest follow-up and was investigated in the "indefinite" group and the CR group. The schedule for endoscopic surveillance for site check is 3 mo after the procedure and then 6 monthly for first year and then yearly thereafter, for 5 years. This outcome considers a patient as one entity, regardless of the number of ESD resections he/she may have had. The change in histological diagnosis pre and post ESD has also been recorded to assess the ability of ESD to influence diagnosis. The histological diagnosis is recorded as the worst histological

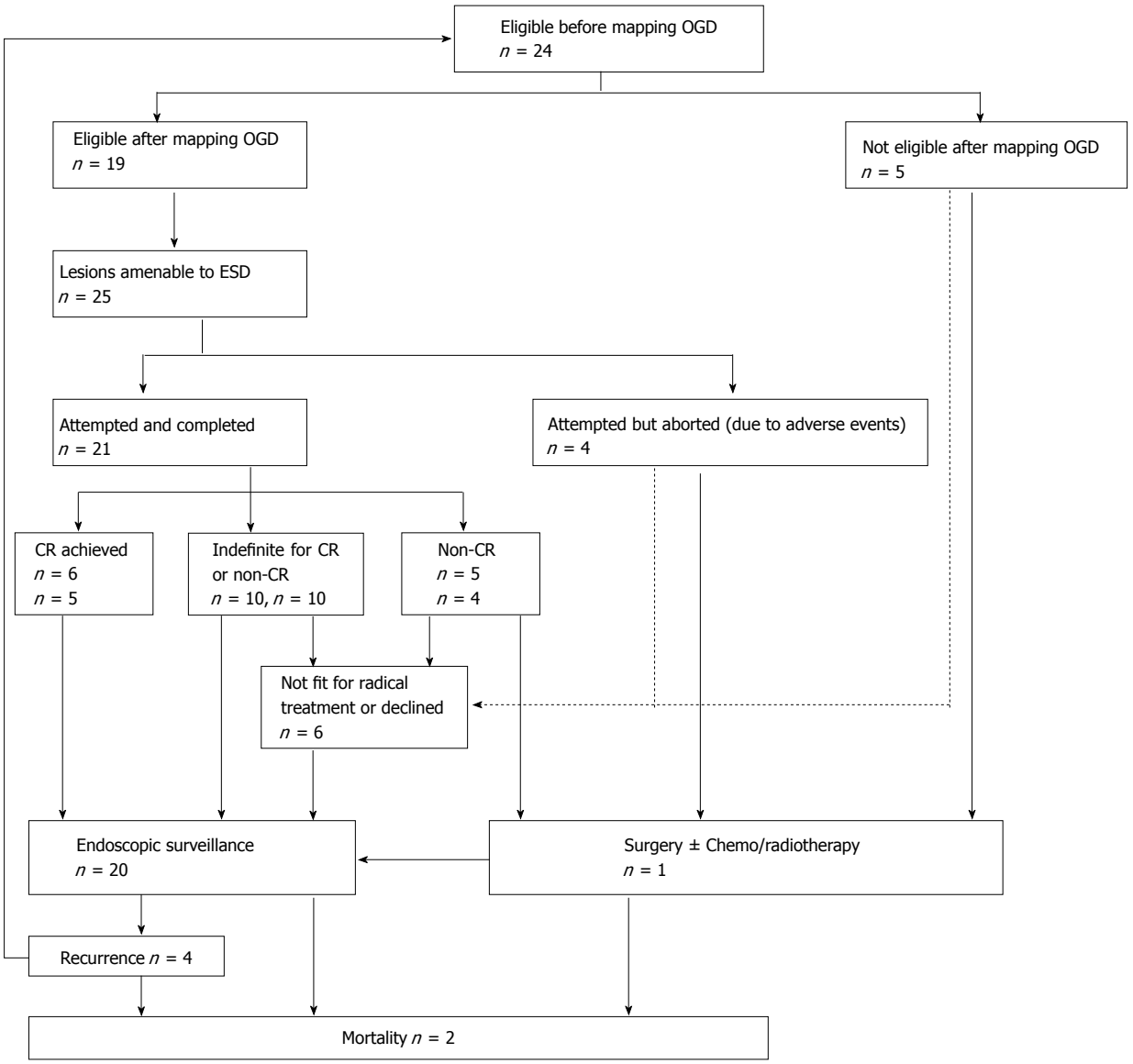

Figure 1 Prisma diagram showing how patients have been selected and their respective outcomes. CR: Curative resection.

grade reported for each lesion.

RESULTS

There were 24 patients with gastric dysplasia and/or neoplasia who were considered for endoscopic treatment using ESD. The demographic data of patients included in the study are shown in Table 1. Out of the 24 patients identified for the study, 19 were deemed suitable for ESD after mapping OGD. ESD was attempted on a total of 25 dysplastic or neoplastic lesions, among which 21 were completed and the patients then followed up or offered further treatment based on histology of the resected specimens, and 4 aborted (Figure 1). There were 5 patients who were found to be unsuitable for ESD after mapping OGD.

Pre-ESD endoscopic assessment

Most lesions were reported as Kato 1, one lesion as Kato 2 and one as Kato 2 to 3. The mean size of lesions resected was 24.7 mm (standard deviation 11.7 mm; range 10-50 mm). Figure 2 shows a lesion suitable for ESD and the procedure in sequence. The main contraindicative features in lesions unsuitable for ESD were ulceration and poor differentiation. Poor lift, large size and deeper invasion constituted other contraindications (Table 2; Figure 2). In one patient, a severe oesophageal stricture prevented passage of the endoscope to assess the lesion. Features of the lesions deemed suitable for ESD are shown in Table 3.

Index procedure: Gastric endoscopic submucosal dissection

Of the 21 resections completed successfully, en-bloc resection was achieved in 71.4% of cases. Resection was considered complete on endoscopy in 90.5% of cases compared to only 38.1% on histology (Table 4). 6 achieved a definite CR (5 patients), 5 were confirmed to

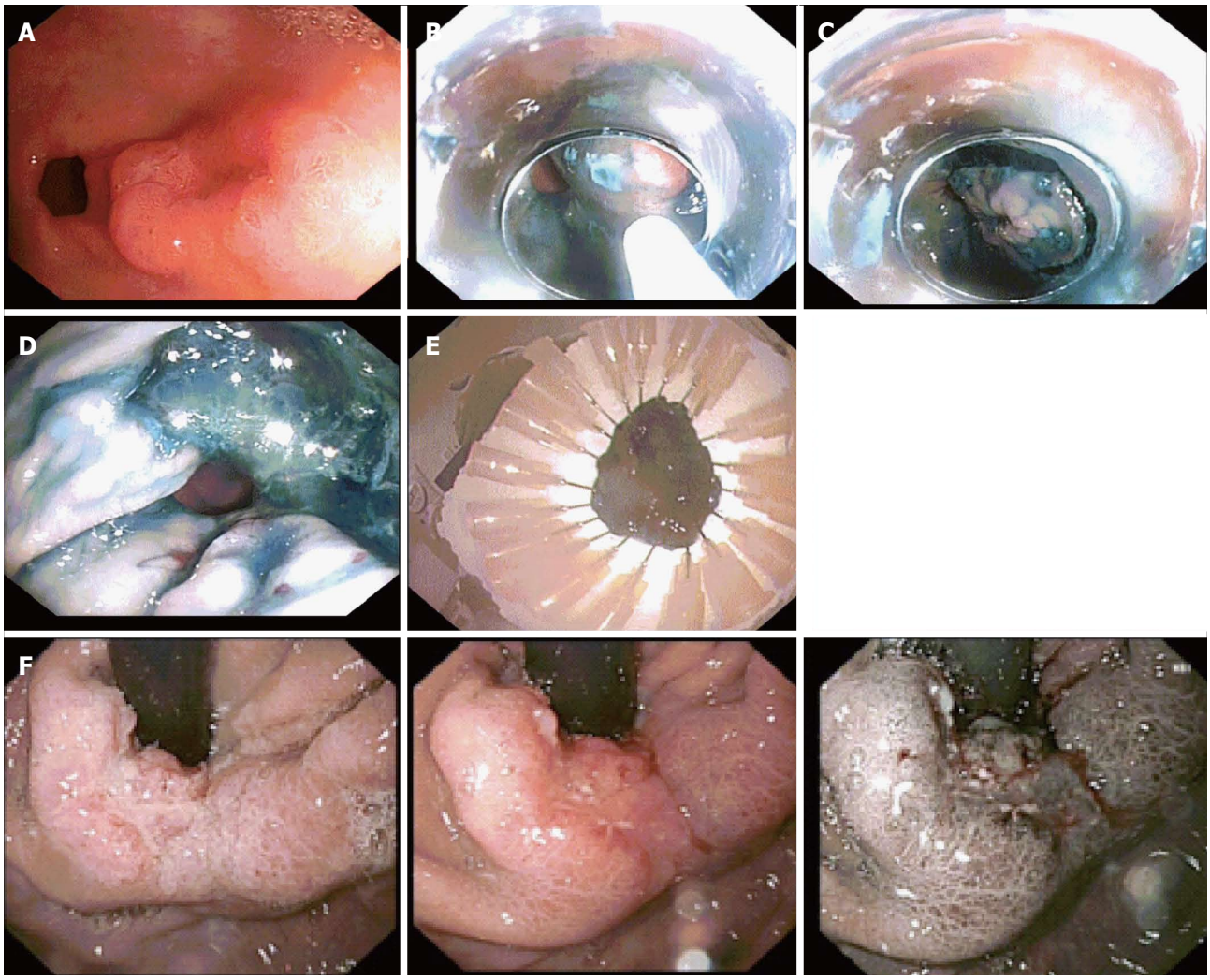

Figure 2 Endoscopic appearance of the gastric lesions considered for resection with endoscopic submucosal dissection. A-E: Macroscopic appearance of lesion with mapping OGD and thus suitable for ESD. This is an area extending from the antrum through to the pyloric ring. The ESD procedure is highlighted here; F: Macroscopic appearance of lesion with suspected sm3 or deeper on mapping OGD and thus unsuitable for ESD. This is an area extending from the cardia through to the upper body. ESD: Endoscopic submucosal dissection.

Table 1 Demographic data of patients included in the study *n* (%)

Variable	Value, *n* = 24
Number of patients assessed for ESD, *n*	24
Age, Mean ± SD, yr	73.0 ± 10.7
Age, range, yr	44-86
Gender, male	20 (83.3)
Gender, female	4 (16.7)
Caucasian ethnicity	24 (100)

ESD: Endoscopic submucosal dissection.

Table 2 Features found to make endoscopic submucosal dissection unsuitable in 5 patients

Patient	Reasons
A	Ulcerated lesion
B	SM3 or deeper invasion; Poorly differentiated lesion
C	Large size: 4-5 cm; Ulcerated over 3 cm
D	Severe oesophageal stricture prevented passage of scope
E	KATO 3; Deeply ulcerated; Poorly differentiated

Table 3 Features of lesions on which endoscopic submucosal dissection has been attempted *n* (%)

Variable	Value, *n* = 25
Location of lesion	
Upper stomach	4 (16)
Mid stomach	7 (28)
Lower stomach	14 (56)
Average of longer axis of lesion (mm)	
Mean ± SD	24.7 ± 11.7
Range	10-50
Histological grade at baseline	
IMC	13 (52)
HGD	8 (32)
LGD	3 (12)
Invasive	1 (4)

LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma.

be non-curative (4 patients) and 10 were indefinite (10 patients) (Figure 3). In the latter group, only 2 patients were considered potential candidates for surgery. The

Table 4 Results of endoscopic submucosal dissection *n* (%)

Variable	Value, *n* = 21
Average number of ESD per patient (including failed ESD)	1.3
Number of en-bloc resections	15 (71.4)
Number of pieces in which lesions were resected	
Mean ± SD	1.5 ± 1.4
Range	1-7
Unspecified but > 1	2
Rate of complete resection on endoscopy	19 (90.5)
Rate of complete resection on histology	8 (38.1)
Margins clear on histology of ESD specimen	
Both VM and HM	8 (38.1)
VM only	1 (4.8)
HM only	1 (4.8)
Neither VM nor HM	1 (4.8)
Not specified or difficult to interpret specimen due to coagulation effect/poor preservation of tissue	10 (47.6)

ESD: Endoscopic submucosal dissection.

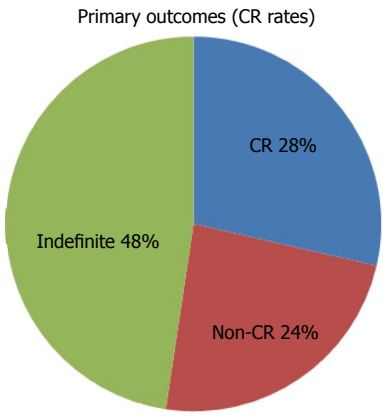

Figure 3 Pie chart showing the rate of primary outcomes: CR (6), non-CR (5) or indefinite (10) when data is inadequate to definitively qualify a resection as CR or non-CR. CR: Curative resection; Non-CR: Non-curative resection.

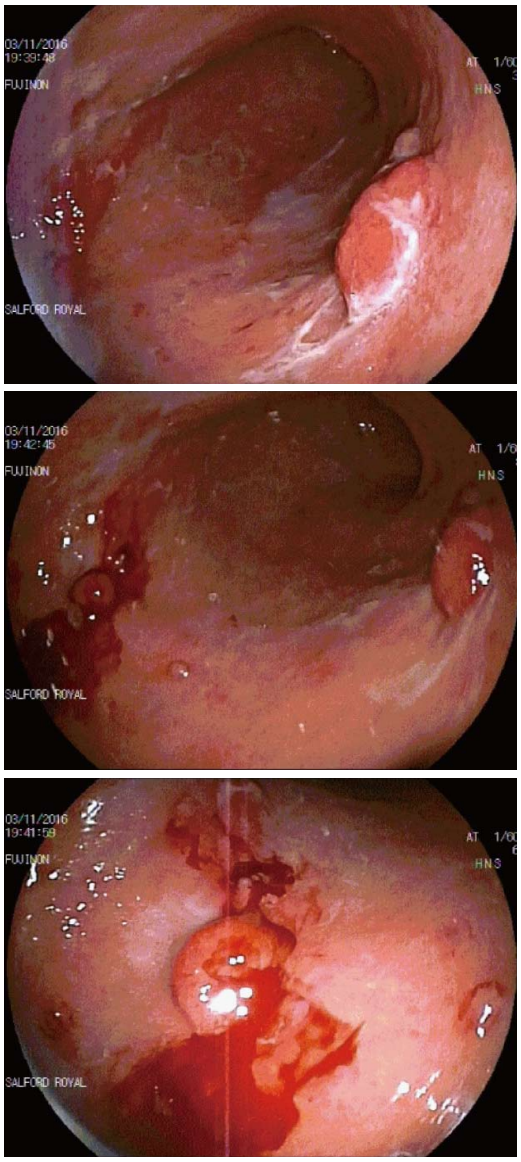

Figure 4 The appearance of the stomach wall on endoscopic follow-up of the patient in which endoscopic submucosal dissection had to be aborted twice due to profuse bleeding. The patient had a high INR and was a poor candidate for ESD at baseline but co-morbidities precluded surgery in his case. Note the 2 metachronous malignant sessile polyps Paris 2a and the marked mucosal friability evident from bleeding. ESD: Endoscopic submucosal dissection.

rest were only offered endoscopic follow-up as complete resection had been achieved on endoscopy and no other poor prognostic features (*e.g.*, poor differentiation) were present. Adjuvant chemo or radio therapy were not given as patients initially selected for this study had no evidence of lymph node involvement or distant metastases on CT and/or PET-CT scans. The histological diagnoses of non-CR patients post ESD are shown in Table 5.

Complications are classified as acute (during the procedure), early (< 48 h after the procedure) or late (> 48 h after the procedure). The most common acute complication reported was oozing small blood vessels (6). In 4 of these cases, bleeding was mild and treated with argon, coagulation forceps or endo-clips. In the other 2, the procedure had to be aborted due to profuse bleeding. Both cases were in the same patient. The patient was on anti-coagulation for atrial fibrillation and had a normal INR after stopping warfarin for 5 d prior to ESD. The marked mucosal friability resulted in bleeding even on mild trauma from the water jet used during endoscopy (Figure 4). A further 2 cases also had to be aborted, one due to the location of the lesion, which would have led to gastric outlet obstruction in due course and the other due to extensive scarring secondary to a previous ESD attempt. There was only one case of early complication involving vomiting within 24 h of the procedure. No cases of late complications were reported.

The median duration of the ESD procedures was found to be 120 min (with factors such as the size of the lesion, its location and tissue factors influencing the length of time required to complete the procedure).

Change in histological grade post endoscopic submucosal dissection

Gastric ESD changed the histological grade in 66.6% of the resected lesions (*n* = 21) (Figure 5), equally

Table 5 Histological grade of 5 non- curative resection

Patient	Histological grade at baseline	Histopathologic diagnosis on ESD specimen of non-CR
A	IMC	IMC with lympho-vascular invasion
A	IMC	Invasive adenocarcinoma; Lympho-vascular invasion
B	IMC	Invasive adenocarcinoma; Poorly differentiated; Diffuse (signet ring) type; Tumour extends into submucosa; Further de-differentiation noted at the invasive aspect
C	Highly suspicious of IMC	Adenocarcinoma with deep margin involvement; Moderately to poorly differentiation; Vascular invasion
D	Invasive adenocarcinoma	Invasive adenocarcinoma; Well differentiated; No lympho-vascular invasion

ESD: Endoscopic submucosal dissection; CR: Curative resection; IMC: Intramucosal carcinoma.

Table 6 Secondary outcome in the cohort' indefinite for curative resection or non- curative resection

Variable	Indefinite, *n* = 10	CR, *n* = 5
Number of patients under endoscopic follow-up, *n* (%)	9 (90)	5 (100)
Median follow-up, mo	2	3
Mean follow-up, mo	5.1	8.5
Range, mo	0-19	0-22
Length of time since ESD, mean ± SD, mo	13.3 ± 11.3	12.2 ± 11.1
Length of time since ESD, range, mo	2 - 38	0 - 26
Number of patients with metachronous or synchronous disease post ESD, *n*	2	0

ESD: Endoscopic submucosal dissection; CR: Curative resection.

downgrading and upgrading the histological diagnoses. Most resected specimens were found to have HGD (5) and IMC (5), compared to the higher proportion of IMC prior to ESD. In addition, as shown in Figure 6, lympho-vascular invasion and invasive cancer were observed in 5 cases compared to only one case pre ESD. Of these 5 cases, 1 resection was found to be completely clear of dysplasia and a further case indefinite for any dysplasia on histology, but with clear evidence of invasion in both cases. LGD was present in 4 cases. In all cases except one, the change in histological grade, if any, was by one stage.

Endoscopic follow-up

In the "indefinite" cohort of 10 patients, one declined further endoscopic follow-up and has been scheduled for a CT scan instead. In addition, 2 patients had not had any follow-up yet at the time of data collection. One passed away 1 mo after his last follow-up endoscopy (the cause of death is unrelated to his gastric diagnosis). The median follow-up period was 2 mo and the mean 5.1 mo for the "indefinite" cohort (Table 6). Complete reversal of dysplasia was observed in 10% and 50% of patients at 12-mo and the latest follow-up respectively in the "indefinite" cohort (Figure 7). Recurrence was observed in 2 patients - both had in fact been considered poor candidates for ESD at baseline due to multiple comorbidities. In the cohort considered to have achieved CR with ESD, 80% were found to be free of dysplasia at their latest endoscopic follow-up at a mean follow-up period of 6.8 mo (Figure 8). Hence, with both cohorts (CR and 'indefinite') combined, 9

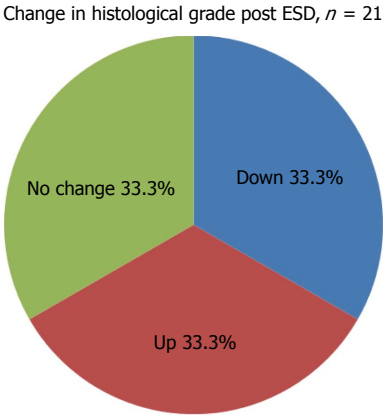

Figure 5 Pie chart showing how endoscopic submucosal dissection changed the histological grade of the resected lesions. Down: Downstaged; Up: Upstaged; ESD: Endoscopic submucosal dissection.

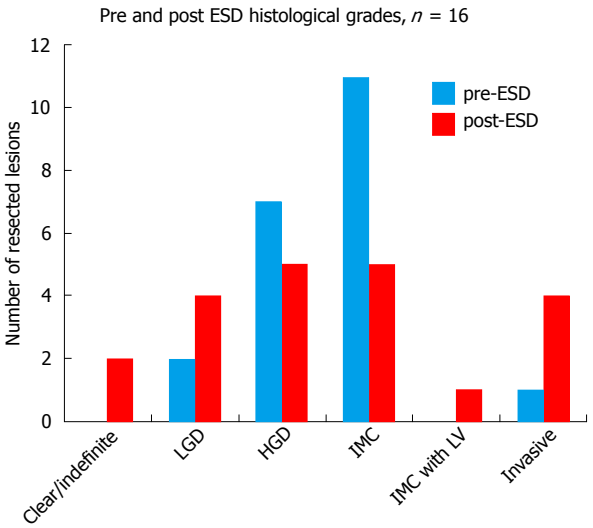

Figure 6 Column chart showing the difference between pre-ESD and post-ESD histological grade for all 16 resected lesions. LGD: Low grade dysplasia; HGD: High grade dysplasia; IMC: Intramucosal carcinoma; LV: Lympho-vascular invasion; ESD: Endoscopic submucosal dissection.

of the 11 patients (81.8%) who had had at least one endoscopic follow-up were found to be free of dysplasia on endoscopy at their latest follow-up at a mean follow-up period of 7.7 mo.

Surgery

Overall, 6 patients were considered for surgery after ESD. In the "indefinite" group, the 2 patients with

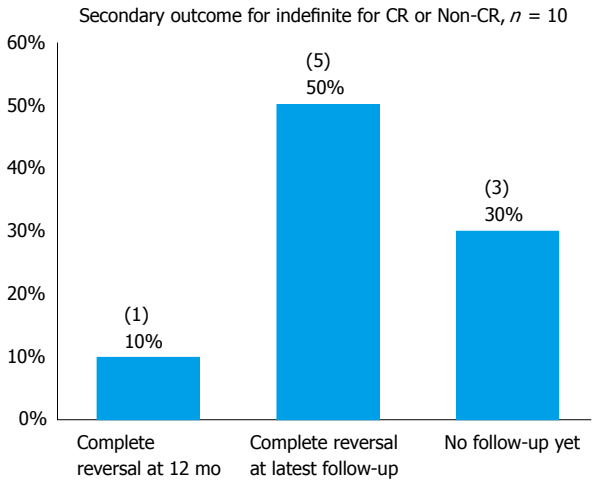

Figure 7 Column chart showing secondary outcomes *i.e.* complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at latest follow-up in the group indefinite for curative resection or non-curative resection post endoscopic submucosal dissection. CR: Curative resection.

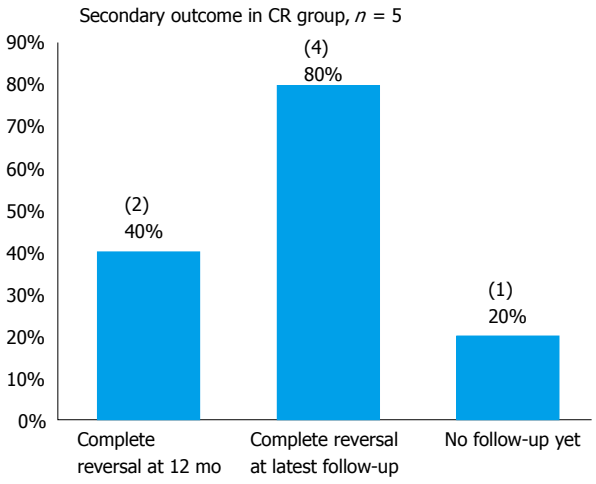

Figure 8 Column chart showing secondary outcomes *i.e.* complete reversal of dysplasia at 12 mo endoscopic follow-up and/or at latest follow-up in the group curative resection post endoscopic submucosal dissection. CR: Curative resection.

recurrence at follow-up were referred for surgery but neither was sufficiently fit to proceed. ESD was attempted again but failed in both patients. They were thus listed for endoscopic surveillance. Metachronous or recurrent polyps were observed at the latest follow-up for both patients at 11 and 19 mo respectively. In the group of 4 patients found to be non-CR, surgery was considered a treatment option in all of them but only one patient was sufficiently fit to proceed with gastrectomy. The rest of non-CR patients were offered either further ESD or endoscopic surveillance or palliative care.

Only 2 of the 5 patients considered unfit for ESD underwent surgery (Patients B and E; Table 2). Post-op staging were pT3N3MxR1 and pT1bN1MxR0 (moderate to poor differentiation) respectively.

Survival rate

One ESD patient died 4 mo after ESD. ESD on this patient was considered curative and endoscopic follow-up at 3 mo post ESD showed no macroscopic recurrence but biopsies could not be taken due to the patient's high INR. Cause of death is unrelated to his primary gastric diagnosis. Survival rate in ESD patients was 94.7% (18 out of 19 patients) at a mean follow-up period of 15 mo.

Another patient in the group found unsuitable for ESD died 5 mo after an attempted mapping OGD. The patient was suffering from a severe oesophageal stricture and was receiving parenteral nutrition. The overall survival rate in the entire cohort was thus 91.7% (22 out of 24 patients).

DISCUSSION

Despite the small sample size, the ability of ESD to achieve CR in carefully selected patients has been demonstrated. Approximately 28% of ESD resections (6) were considered curative. Moreover, 4 of the 5 CR patients were free of dysplasia at the latest follow-up while the fifth patient had not had any follow-up yet, thus corroborating previous studies that demonstrated the positive long-term outcomes in patients with a CR, as defined by the JGCA criteria.

Positive long-term outcomes were also observed in a large proportion of the "indefinite" patients, despite the inability to confirm CR on histology. In the 2 patients who had recurrence of disease, histological evaluation of the ESD specimens had been particularly challenging due to marked inflammation in one case and very severe distortion of the tissue in the other. The specimen in fact reached the pathology laboratory outside formalin. Non-CR could therefore not be confidently excluded in these 2 patients and was in fact made more likely by a pre-ESD diagnosis of IMC. It was clear however on endoscopic follow-ups that these 2 patients had more advanced disease than suspected prior to ESD, as suggested by the presence of several metachronous and/or synchronous - polyps. Overall, despite the inability to always confirm CR on histology, gastric ESD has proven itself highly effective at clearing neoplastic growth if complete resection can be achieved on endoscopy. It also points to the importance of MDT discussions to avoid unnecessary surgery in patients indefinite for CR or non-CR.

The main reason for uncertainty regarding the completeness of excision on histology was the poor preservation of the resected specimens. In many instances, the specimen had been pinned down too deeply into the polystyrene board thus inflicting substantial trauma to the tissue. Other artefacts such as diathermy changes at the periphery, excision margins not clearly defined and inflammation also hindered accurate interpretation. In one case, the lesion had to be resected piecemeal. Other reasons included missing report and lack of mention of margin clearance. Hence, it is clear that to allow for the efficacy of ESD to be more accurately investigated in the future, ways

to satisfactorily preserve the resected specimen in its original state and implementing a more systematic approach to reporting histological findings are required.

This study also demonstrates the importance of careful selections of patients at baseline. Out of the 5 non-CR resections, 3 already contained poor prognostic features at baseline. However, the MDT consensus was to proceed with ESD given the patients' multiple co-morbidities that made them unfit for surgery. In one case, poor differentiation was seen prior to ESD while in the other two, invasive carcinoma had been identified. In the rest of non-CR cases, deeper invasion would have been left unnoticed had the lesion not been resected by ESD. ESD effectively identified lympho-vascular invasion in these 2 lesions presumed to be IMC only prior to ESD. This observation lends support to the status of ESD as the only definitive tool to exclude invasion. Moreover, ESD changed the histological grade in 66.6% of resected lesions. Unlike more large-scale studies however, ESD equally downgraded and upgraded histological diagnoses. In one exceptional case, the histological grade changed from IMC pre-ESD to clear of any dysplasia or malignancy post ESD. Further investigations into this case revealed observer bias in the interpretation of pre-ESD biopsy specimen at the patient's local hospital. ESD thus enabled the correct diagnosis to be made. This however points to a potential source of error in this study, *i.e.,* bias in interpretation of histology slides.

Only one patient underwent surgery after a non-CR ESD. Interestingly, in this patient, the ESD scar was still present on endoscopic follow-up after the surgery. Deep biopsies taken from this site were all found to be clear of dysplasia, even at the latest endoscopy performed 30 mo post ESD. In this patient, ESD had revealed a well-differentiated invasive adenocarcinoma without any lympho-vascular invasion. This "invasion" constituted the indication for surgery even though the exact depth of invasion was not reported. Hence, it may be possible that ESD patients are being unnecessarily referred for surgery and that ESD alone could be sufficient to treat more advanced diseases with the advantage of shorter hospital stays and fewer complications.

Some of the other limitations of this study include relatively short follow-up periods preventing more accurate assessment of the long-term outcomes and potential bias in letters and endoscopy reports. Hence we plan to study a larger number of patients and have a longer follow-up period in order to reduce bias and truly assess the efficacy of ESD in our Caucasian United Kingdom population.

In conclusion, these results although modest are promising and provide early evidence in favour of the use of ESD in Caucasian populations in the United Kingdom. Despite the wealth of evidence for the efficacy of gastric ESD in Far Eastern countries, the National Institute of Health and Care Excellence (NICE) United Kingdom still views upper GI ESD as a procedure to be applied on a case-by-case basis only with an MDT approach[22], thus demonstrating the need for further, larger-scale studies into this technique in the United Kingdom and other Western countries.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is a minimally invasive technique used to treat early superficial lesions of the gastrointestinal tract. It is popular in Far East countries where its outstanding efficacy has been proven by multiple studies. Technological advances have recently made ESD more accessible worldwide. In the United Kingdom, this intervention is still relatively new and local evidence to support its use still scarce.

Research motivation

This study aims to evaluate the application of ESD in Caucasian patients in the United Kingdom and seeks to compensate for the lack of evidence in the literature in favour of its use in this country. Larger scale studies will be required in the future.

Research objectives

This study constitutes a step forward in providing the evidence necessary to support the application of ESD among Caucasian patients in the United Kingdom as well as to help produce standardised clinical guidelines to inform local clinical practice for this relatively new intervention.

Research methods

This retrospective study uses data obtained from the Department of Gastro-enterology at Salford Royal NHS Foundation Trust in the United Kingdom, a tertiary centre for gastrointestinal interventions. Data for a period of 2 years has been analysed using Microsoft Excel.

Research results

Of the 21 lesions resected with ESD, 6 achieved curative resection (CR), 10 were "indefinite" for CR or non-CR, and 5 were considered non-CR. A favourable long-term outcome was observed in the CR and "indefinite" groups, with clearance of dysplasia observed overall in 81.8% of patients who had had at least one endoscopic follow-up. ESD also changed the histological diagnoses in 66.6% of cases. These results are promising and provide early evidence in favour of the use of ESD in the United Kingdom.

Research conclusions

ESD as applied to Caucasian patients in the United Kingdom can produce promising results as shown by this study. There have not been similar studies in the United Kingdom in the past and thus larger scale studies are required to fully evaluate the efficacy and safety profile of ESD as applied to upper gastrointestinal cancers.

Research perspectives

To better assess the effectiveness of ESD at clearing early neoplastic lesions of the stomach and other upper gastrointestinal cancers among Caucasian patients in the United Kingdom, a prospective study involving a larger sample of such patients is required.

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ORIGINAL ARTICLE

Observational Study

Lumen-apposing metal stents for benign gastrointestinal tract strictures: An international multicenter experience

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Abstract

AIM

To investigate technical feasibility, outcomes and adverse events of the lumen-apposing metal stent (LAMS) for benign gastrointestinal (GI) tract strictures.

METHODS

Between July 2015 and January 2017, patients undergoing treatment by LAMS for benign GI strictures at

three tertiary referral centers were included in this study. Primary outcomes included technical success, short-term clinical success, long-term clinical success, and adverse events. Short-term clinical success was defined as symptom resolution at 30 d after stent placement. Long-term clinical success was defined by symptom resolution at 60 d in patients who continued to have indwelling stent, or continued symptom resolution at 30 d after elective stent removal.

RESULTS

A total of 21 patients (mean age 62.6 years, 47.6% males) underwent placement of LAMS for benign GI strictures. A 15 mm × 10 mm LAMS was placed in 16 patients, a 10 mm × 10 mm LAMS was placed in 2 patients, and a 16 mm × 30 mm LAMS was placed in 3 patients. Technical success was obtained in all cases. Short-term clinical success was achieved in 19 out of 21 cases (90.5%), and long-term clinical success was achieved in 12 out of 18 (66.7%). Mean (range) stent indwell time was 107.2 (28-370) d. After a mean (range) dwell time of 104.3 (28-306) d, 9 LAMSs were removed due to the following complications: ulceration at stent site (n = 1), angulation (n = 2), migration (n = 4) and stricture overgrowth (n = 2). Migration occurred in 4 cases (19.0%), and it was associated with stricture resolution in one case. Median (range) follow-up period was 119 (31-422) d.

CONCLUSION

Utilization of LAMS for benign strictures has shown to be technically feasible and safe, but adverse events highlight the need for further study of its indications.

Key words: Endoscopy; Stent; Gastrointestinal diseases; Stricture; Biomedical technology

Core tip: Treatment of benign short gastrointestinal (GI) tract strictures has primarily involved endoscopic balloon dilation, intralesional steroid injection and the conventional fully-covered metal stent. The lumen-apposing metal stent (LAMS), which has been used to drain pancreatic fluid collections, may serve as a more effective alternative. This study measures technical feasibility and potential short and long-term effectiveness of LAMS for benign GI strictures at three tertiary referral centers. Although results are promising, complications include angulation, stricture overgrowth and ulceration at stent site. These highlight the need for further study to better specify which patients should receive LAMS and how to minimize burden of complications.

Santos-Fernandez J, Paiji C, Shakhatreh M, Becerro-Gonzalez I, Sanchez-Ocana R, Yeaton P, Samarasena J, Perez-Miranda M. Lumen-apposing metal stents for benign gastrointestinal tract strictures: An international multicenter experience. *World J Gastrointest Endosc* 2017; 9(12): 571-578 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i12/571.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i12.571

INTRODUCTION

Benign etiologies of gastrointestinal (GI) strictures include ulcers, caustic ingestion, post-operative anastomotic states and inflammation[1]. The management of benign GI strictures has typically entailed endoscopic balloon dilation (EBD). However, EBD often does not provide definitive treatment and carries risks of bleeding and perforation[2,3]. Intralesional steroid injections may serve as an adjunct to endoscopic dilation that leads to increased efficacy of dilation and decreased number of total dilations[4]. Conventional fully-covered self expandable metal stent (cSEMS) has offered an alternative for therapy in cases that are refractory to EBD and steroid injections[5,6]. The cSEMS holds advantages over uncovered and partially-covered stents due to the relative ease of deployment and retrieval[7]. Furthermore, cSEMS may provide a gradual and continuous dilation of the stenotic segment. However, the use of cSEMS has demonstrated high rates of migration that may occur early in the period after stent placement, which may ultimately compromise long-term clinical success. Endoscopic suturing of cSEMS to tissue has been a recent advance that has mitigated this issue of migration[8], but this procedure is expensive and can be technically challenging[9].

Recently, lumen-apposing metal stents (LAMS) have become widely available for drainage of pancreatic fluid collections that exhibit lumen-apposing and dual anchoring capabilities[10]. These design features allow for robust pseudocyst drainage and the passage of an endoscope with a lower risk of stent migration due to anchoring. The AXIOS™ stents (Boston Scientific, Marlborough, United States) are 10 mm in saddle length, 10 mm or 15 mm in diameter, and with flanges that are 21 mm or 24 mm in diameter.

The NAGI™ stent (Taewoong Medical Co., Ltd., Ilsan, South Korea) is another type of LAMS that has been feasible in treating both pancreatic pseudocysts and walled-off necrosis. The presence of flared edges allows for its dual-anchoring capabilities, and the inclusion of a retrieval string also facilitates the removal of the stent. These LAMS are 10-30 mm in length, 10-16 mm in diameter, and contain flared edges 20 mm in diameter. Overall, the dimensions of the AXIOS™ and NAGI™ stents allow for potential use in treating short-length strictures that are less than or equal to 10 mm with a low risk of migration due to the anchoring flanges.

Prior studies have thus far supported LAMS as a potentially safe and effective measure to treat benign GI strictures (Table 1). Majumder *et al*[11] demonstrated that in a group of 5 patients, the placement of AXIOS™ stent led to successful resolution of symptoms with no stent-related adverse events during a median follow-up period of 120 d. Irani and colleagues found that in a

Table 1 Summary of prior studies on lumen-apposing metal stent for benign strictures *n* (%)

	Majumder *et al*[11] (2015)	Irani *et al*[12] (2016)	Yang *et al*[13] (2017)
Total cases	5	25	30
Age	47.4 (mean)	54 yr (median)	51.6 (mean)
Females	4 (80.0)	18 (72.0)	19 (63.3)
Underwent prior endoscopic dilation	3 (60.0)	20 (80.0)	27 (90.0)
Prior cSEMS	1 (20.0)	1 (4.0)	8 (29.6)
LAMS used			
AXIOS 15 mm × 10 mm	5 (100.0)	25 (100.0)	29 (96.7)
AXIOS 10 mm × 10 mm	0	3 (12.0)[1]	1 (3.3)
Technical success	Not described	25 (100)[2]	29 (96.7)[3]
Clinical success	Not described		
Short-term		15 (60)[4]	27 (90.0)[5]
Long-term			19 (82.6)[6]
Migration	0	2 (7.0)	2 (8.0)
Median stent dwell time (range)	Not described	92 d (3-273, median)	Not described
Median follow-up, d (range)	120 (84-140)	301 (62-681)	100 (60-139)

[1]Three patients initially had an AXIOS 10 mm × 10 mm placed, which was immediately upsized to 15 mm × 10 mm; [2]Technical success was defined as appropriate stent placement across the stricture verified endoscopically and fluoroscopically; [3]Technical success was defined as successful placement of the LAMS across the stricture; [4]Clinical success was defined as resolution of underlying symptoms for at least 6 mo after stent placement; [5]Short-term clinical success was defined as symptom improvement/resolution with indwelling stent; [6]Long-term clinical success was defined as symptom improvement/resolution after stent removal. LAMS: Lumen-apposing metal stent.

group of 25 patients with benign GI strictures refractory to standard therapies, the placement of AXIOS™ stent led to resolution of symptoms at 6 mo in 60.0% of cases[12]. Yang *et al*[13] demonstrated in a group of 30 patients, an indwelling AXIOS™ stent led to resolution of symptoms in 90.0% of cases, and 82.6% continued to have improved symptoms after LAMS removal. The data remains limited, and the prior studies solely involve the AXIOS™ stent. We describe the feasibility, safety and efficacy of treating benign GI strictures with two types of LAMS in an international multicenter setting.

MATERIALS AND METHODS

Between July 2015 and January 2017, patients who had undergone treatment by LAMS for benign GI strictures at three tertiary referral centers were identified. All cases were reviewed for demographic information, clinical presentation, initial diagnosis, anatomic location and prior endoscopic therapies. Inclusion criteria were patients with benign strictures that were not amenable to placement of cSEMS or had failed prior endoscopic therapies.

Primary outcomes evaluated included technical success, short-term clinical success, long-term clinical success, and adverse events. Technical success was defined by appropriate stent placement across the stricture verified endoscopically and fluoroscopically. Short-term clinical success was defined as symptom resolution at 30 d after stent placement, inclusive of patients with indwelling stents at day 30 and patients who had elective removal prior to day 30. Long-term clinical success was defined by symptom resolution at 60 d in patients who continued to have indwelling stent, or symptom resolution at 30 d after elective stent removal. Early complications were defined by adverse events pertaining to the stent that occurred either at the time of placement or within 24 h after placement. Late complications were defined by adverse events pertaining to the stent that occurred after 24 h the stent was verified to be placed. Follow-up of stent placement took place *via* clinic visits, telephone calls, imaging studies and endoscopic surveillance appointments.

RESULTS

A total of 21 patients (mean age 62.6 years, 47.6% males) underwent placement of LAMS for benign GI strictures over the study period at the three centers (Table 2). Anatomic location of strictures included proximal esophagus (5, 23.8%), distal esophagus (4, 19.0%), stomach (6, 28.6%), duodenum (4, 19.0%), and colon (2, 9.5%). Etiology of GI strictures in this study included prior surgical anastomosis (10, 47.6%), prior surgical anastomosis and radiation therapy (4, 19.0%), caustic injury (3, 14.3%), peptic strictures (3, 14.3%) and chronic pancreatitis (1, 4.8%). Sixteen patients (76.2%) had at least one prior endoscopic therapy, which included EBD (n = 14), placement of cSEMS (n = 3), and stricturoplasty (n = 1).

In all cases, procedures were performed using a forward-viewing therapeutic endoscope. A standard guidewire was passed across the stricture under fluoroscopic guidance and contrast may have been utilized *via* injection to confirm stricture length. Upon the discretion of the endoscopist, the decision was made to use an AXIOS™ stent of 10 or 15 mm in diameter, or a NAGI™ stent measured at 16 mm × 30 mm (Figure 1). The LAMS were deployed under fluoroscopic and endoscopic guidance.

A 15 mm × 10 mm LAMS was placed in 16 patients, a 10 mm × 10 mm LAMS was placed in 2 patients,

Table 2 Demographics and stricture characteristics

	Proximal esophagus (*n* = 5)	Distal esophagus (*n* = 4)	Stomach (*n* = 6)	Duodenum (*n* =4)	Colon (*n* = 2)	Total (*n* = 21)
Age, mean (yr)	54	68.5	59	65.8	77	62.6
Gender						
Male	3 (60.0)	3 (75.0)	2 (33.3)	2 (50.0)		10 (47.6)
Female	2 (40.0)	1 (25.0)	4 (66.7)	2 (50.0)	2 (100.0)	11 (52.4)
Etiology						
Post-surgery/radiation	4 (80.0)	3 (75.0)	4 (66.7)	1 (25.0)	2 (100.0)	14 (65.2)
Peptic			1 (16.7)	2 (50.0)		3 (13.0)
Chronic pancreatitis				1 (25.0)		1 (4.3)
Caustic ingestion	1 (20.0)	1 (25.0)	1 (16.7)			3 (13.0)
Types of prior treatments						
Balloon dilatation						
1			1	1	1	3
2	4	2	2			8
3			1		1	2
> 3		1				1
Fully-covered stents	1	1		1		3
Prior migration	1	1		1		3
Stricturoplasty	1					1

Table 3 Results of lumen-apposing metal stent placement

	Proximal esophagus (*n* = 5)	Distal esophagus (*n* = 4)	Stomach (*n* = 6)	Duodenum (*n* =4)	Colon (*n* = 2)	Total (*n* = 21)
LAMS						
15 mm × 10 mm AXIOS	5 (100.0)	2 (50.0)	3 (50.0)	4 (100.0)	2 (100)	16 (76.2)
10 mm × 10 mm AXIOS			2 (33.3)			2 (9.5)
16 mm × 30 mm NAGI		2 (50.0)	1 (16.7)			3 (14.3)
Mean stent dwell time (d)	67.6	56.5	151.2	167.5	55.5	107.2
Technical success	5 (100.0)	4 (100.0)	6 (100.0)	4 (100.0)	2 (100)	21 (100.0)
Clinical success						11
Short-term	5 (100.0)	3 (75.0)	5 (83.3)	4 (100.0)	2 (100)	19 (90.5)
Long-term	1 (25.0)	2 (66.7)	5 (100.0)	3 (75.0)	1 (50.0)	212 (66.7)
Reasons for stent removal						
Angulation	1	1				2
Stent migration	1	1		2		4
Stricture overgrowth			2	1		2
Ulceration			1			1
Resolution	1			11		3
Treatments after stent failure						
Balloon dilation		2				2
cSEMS	1					1
15 mm × 10 mm AXIOS		1	1	1		3
16 mm × 30 mm NAGI	2	1				3

and a 16 mm × 30 mm NAGI stent was placed in 3 patients (Table 3). Technical success was obtained in 21 out of 21 cases (100.0%). Short-term clinical success was achieved in 19 out of 21 cases (90.5%) (Figure 2). Long-term clinical success was achieved in 12 out of 18 (66.7%). Three cases did not qualify for evaluation for long-term clinical success due to: Currently indwelling at a period of less than 60 d or a period of less than 30 d after already electively removed. Mean (range) dwell time of all cases was 107.2 (28-370) d.

There were no early adverse events in any of the cases such as bleeding or perforation. There were no serious delayed adverse events in any of the cases. However, after a mean (range) dwell time of 104.3 (28-306) d, 11 LAMS (52.4%) needed to be removed due to the following complications: Ulceration at stent site (*n* = 1), angulation (*n* = 2), migration (*n* = 4), tissue overgrowth (*n* = 2), and stricture resolution (*n* = 3). Two patients with LAMS removal did not require further intervention. Overall, there were four cases (19.0%) that involved migration; in one of the cases, it was found that migration occurred likely due to resolution of the stricture. In the 8 cases in which the patients continued to be symptomatic after LAMS removal, the patients underwent repeat dilation, placement cSEMS or repeated placement of LAMS. Median (range) follow-up period was 119 (31-422) d.

Stent placement by site

Of the 5 proximal esophageal strictures, 4 (80.0%)

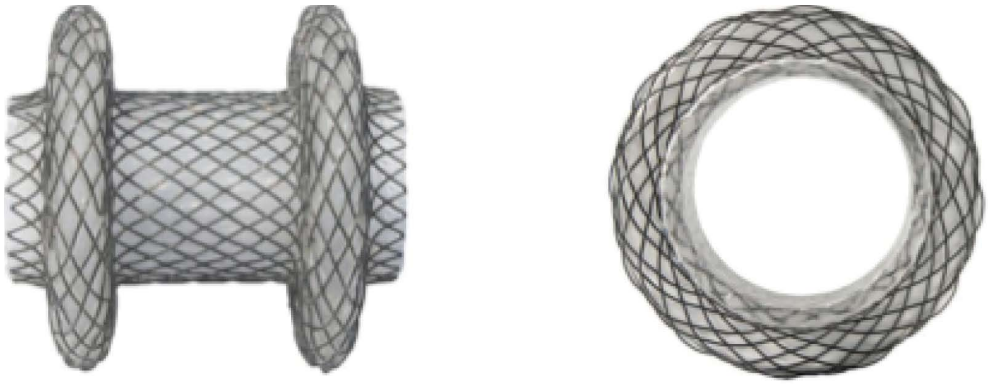

Figure 1 AXIOS™ stent and delivery system.

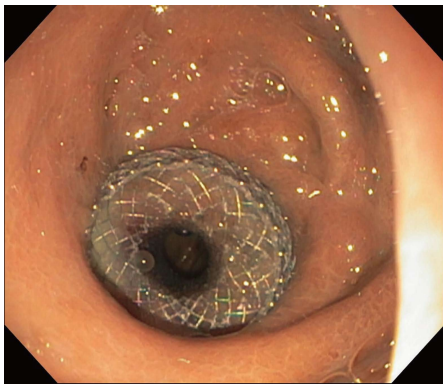

Figure 2 AXIOS™ 15 mm × 10 mm stent across gastrojejunal anastomotic stricture.

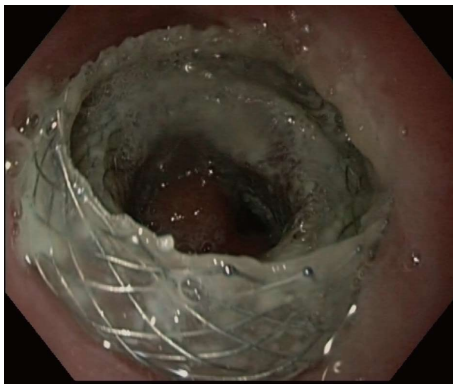

Figure 3 Angulation of AXIOS™ 15 mm × 10 mm that was placed across a distal esophageal anastomotic stricture.

were due to prior surgical anastomosis and 1 (20.0%) was due to caustic ingestion. All five underwent prior treatments that included balloon dilatation and placement of cSEMS, which were complicated by recurrence and migration, respectively. All five underwent placement of 15 mm × 10 mm AXIOS™ LAMS. All five cases achieved technical success. All five cases (100.0%) achieved short-term clinical success. One case did not qualify for long-term clinical success evaluation because the patient had an indwelling LAMS less than 60 d. Only one of the remaining four (25%) cases achieved long-term clinical success. The first case that did not meet long-term clinical success involved removal of an AXIOS™ stent after indwell time of 90 d due to perceived resolution of stricture; however, it was found that the stricture had recurred. The second case that did not meet long-term clinical success involved an AXIOS™ stent that had distally migrated after 110 d. The third case that did not meet long-term clinical success involved an AXIOS™ stent that had angulation at stent site after 40 d, in which the lumen of the stent was abutting the oesophageal wall (Figure 3). This led to odynophagia and vomiting that necessitated removal of LAMS.

Of the 4 distal esophageal strictures, 3 (75%) were due to prior surgeries and 1 (25.0%) was due to caustic ingestion. Three (75%) underwent prior therapies including balloon dilatation and placement of cSEMS, which were complicated by recurrence and migration, respectively. Two underwent placement of 15 mm × 10 mm AXIOS™ LAMS, and two underwent placement of 16 mm × 30 mm NAGI™ LAMS. All four cases achieved technical success. Three (75%) achieved short-term clinical success. The one case that did not achieve short-term clinical success was due to a NAGI™ stent that migrated prior to 30 d after stent placement, leading to recurrent symptoms and removal of the stent; thus, this case did not qualify for long-term success evaluation. Two out of the remaining three cases (67%) achieved long-term clinical success. The one case that did not achieve long-term clinical success was due to angulation of a 15 mm × 10 mm AXIOS™ LAMS at the stent site that occurred 45 d after stent placement, which led to vomiting and subsequent removal of the stent.

Of the 6 gastric strictures, 4 (67.7%) were due to prior surgery, 1 (16.7%) was due to caustic injury, and 1 (16.7%) was due to peptic ulcer. Three (67.7%) underwent prior therapy, which was balloon dilation that failed due to recurrence. Three underwent placement of 15 mm × 10 mm AXIOS™ LAMS, two underwent placement of 10 mm × 10 mm AXIOS™ LAMS, and one underwent placement of NAGI™ LAMS. All 6 stent placements achieved technical success. Five (83.3%) achieved short-term clinical success. One (16.7%)

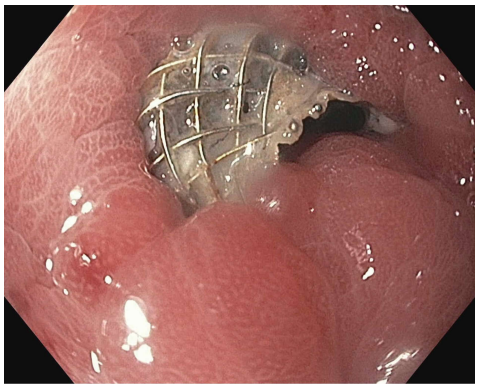

Figure 4 Stricture overgrowth of AXIOS™ 10 mm × 10 mm that was placed across a gastrogastric anastomotic stricture.

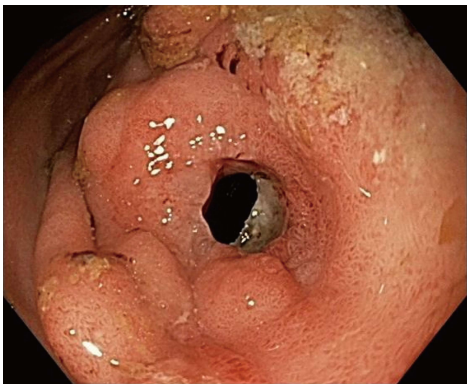

Figure 5 Stricture overgrowth of AXIOS™ 10 mm × 10 mm that was placed across a prepyloric stricture.

placement of 15 mm × 10 mm LAMS was complicated by an ulcer at 28 d, requiring removal of LAMS; thus, this case did not qualify for long-term clinical success evaluation. The remaining five cases achieved long-term clinical success. Of note, one case involved a patient that developed tissue overgrowth at the site of a 10 mm × 10 mm AXIOS™ stent placement across a gastrogastric anastomotic stricture after 306 d, which resolved with stricturoplasty (Figure 4). Another case involved a patient that developed tissue overgrowth at the site of a 10 mm × 10 mm AXIOS™ stent placement across a prepyloric anastomotic stricture after 183 d, which led to stent removal (Figure 5).

Of the 4 duodenal strictures, 2 (50%) were peptic ulcer disease, 1 (25%) was due to chronic pancreatitis, and 1 (25%) was an anastomotic stricture from prior Whipple procedure. Two (50%) underwent prior therapies including balloon dilatation and placement of cSEMS, which failed due to recurrence and migration, respectively. All four cases underwent placement of 15 mm × 10 mm AXIOS™ LAMS. All cases achieved technical success and short-term clinical success. Three (75%) cases achieved long-term clinical success. The one case that failed to achieve clinical success was due to proximal migration of AXIOS™ stent that occurred after an indwell time of 150 d, requiring the placement of another AXIOS™ stent. Of note, another case resulted in distal migration of AXIOS™ stent after 60 d. However, upon removal of this stent, the stricture was resolved and no further intervention was needed.

Of the 2 colonic strictures, both were due to prior surgical anastomosis. Both underwent prior treatments with balloon dilatation, which failed due to stricture recurrence. Both underwent placement of 15 mm × 10 mm AXIOS™ LAMS. Technical and clinical successes were obtained in both cases. One case (50%) involved elective removal after indwell time of 48 d due to resolution of the stricture, and patient has been asymptomatic since LAMS removal.

DISCUSSION

The management of benign GI strictures is often challenging due to the refractory nature of these strictures and failure of conventional therapy, EBD. In our study, the majority of patients who underwent LAMS for benign strictures received prior therapies that failed. Those who had prior EBD or stricturoplasty had developed stricture recurrence, and prior placement of cSEMS had led to migration. These complications are consistent with those that have been previously described[2,3,8]. A recent systematic review and meta-analysis on outcomes following stent placement in refractory benign esophageal strictures reported an overall stent migration rate of 28.6%[14]. In order to prevent the occurrence of migration associated with cSEMS, the utilization of stent suturing as a means of fixation has been described. The use of this external fixation method has been associated with lower migration rates[15]. However, stent suturing with cSEMS is also described to be associated with stricture overgrowth. Furthermore, stent suturing involves a more technically challenging approach for the endoscopist that may affect technical success and feasibility.

In our study, the decision was made to proceed with LAMS prior to considering surgical intervention. Although surgery may provide an opportunity to definitively treat benign strictures, rates of postoperative morbidity and mortality are significant[16-18]. Among the population predisposed to developing benign GI strictures, the risk of surgery is compounded by advanced age, poor nutritional status and other related comorbidities among these patients.

For strictures that are refractory to standard endoscopic therapies, we thus would recommend further consideration of endoscopic therapies, in which LAMS may serve as a feasible and safe alternative. Given the length parameters of LAMS, currently LAMS would be appropriate for benign, short strictures. Specifically, this would be for strictures < 10 mm in length for utilization of AXIOS™ LAMS and < 30 mm in length for utilization of NAGI™ LAMS.

In contrast to the conventional SEMS, LAMS imparts lumen apposition *via* its wide flanges and provides anchorage, hence potentially reducing the risk of stent migration. In our study, the migration rate for those

who underwent LAMS placement was 19.0% and this does appear to be higher than other studies on this topic. In the cases of LAMS migrating, the mean period of time before detected migration was 87.5 d, which appears to be a potentially longer period in comparison to the period associated with cSEMS migrating in our experience. Nonetheless, it is important to highlight that migration may occur with LAMS use, as this has not been a common observation in prior studies.

Overall, technical success was achieved in all cases without incidence of any immediate complications. Of note, all stents were placed by interventional endoscopists that were highly experienced in endoscopic stent placement. There were also no difficulties with evaluation of the stented area or removal of the stent. This supports the feasibility of endoscopic follow-up and surveillance in patients with indwelling LAMSs.

This study supports the high short term clinical success rate found in previous case series[12,13]. We chose 30 d after stent placement to be the measure of short term clinical success as recurrent strictures are defined as those unable to maintain a satisfactory luminal diameter for this length of time[19]. The long term clinical success rate in this series fell quite dramatically however largely due to complications occurring after 30 d. The rate of complications in this study that prevented short or long-term clinical success was high relative to other studies at 38.0%[12,13]. Furthermore, we noted complications not mentioned in the literature previously. In addition to migration, we found angulation to be a potential complication, at a rate of 9.5%. This involved the stent lumen/axis of the LAMS being misaligned within the luminal GI tract. Due to the stent lumen facing the luminal walls, patients developed foreign body sensation and obstructive symptoms. In these cases, this likely occurred due to the short length of LAMS coupled with the angled nature of these particular anastomotic strictures. Therefore, assessment of the stricture angle in relation to adjacent lumen may be an important factor when considering LAMS as a potential therapeutic option. Stricture overgrowth was also encountered in this study as a late complication. In our study, there were two cases of tissue overgrowth leading to stent dysfunction. Of note, one case had the stent placed for 183 d and the other 306 d. In one case, stricturoplasty of the tissue overgrowth with needle knife was successful in recanalizing the stent. In another case, the stent was removed and the stricture has since remained patent. The duration of stent dwell time of these cases was much longer than the mean dwell time of this series which might indicate that a scheduled assessment of the LAMS should occur at a specified duration after placement, possibly 180 d, to ensure tissue overgrowth is not occurring.

Limitations of this study include its retrospective nature with lack of a control arm, lack of symptom severity score, and no standardized method of managing complications. Given the lower volume of benign refractory GI strictures relative to other GI pathological processes, it would be difficult to have a robust control arm for analysis. The utilization of a symptom severity score may have also allowed for ability to better categorize the treatment effect. This data would potentially add clinical significance to our evaluation of LAMS, as we would not only categorize how many patients benefited, but also to the extent of symptom improvement. Lastly, the cases took place in 3 different tertiary care centers with no standardized algorithm of stent management. As a result, decisions of clinical and endoscopic follow-up as well as decisions regarding management of stent related complications were made at the endoscopists' discretion and best judgment.

In conclusion, we found that the utilization of LAMS is technically feasible and safe as a primary or salvage therapy for benign GI strictures with a high short term clinical success rate. However, late complications related to stricture overgrowth, stent migration, and angulation prevented a sustained symptom-free period in a large proportion of cases. These adverse events highlight the need for further study in this area to better understand which patients and which strictures are most optimal for management with LAMS prior to widespread adoption of this technique for the treatment of benign GI strictures.

COMMENTS

Background

Treatment of benign short gastrointestinal (GI) tract strictures has primarily involved endoscopic balloon dilation, intralesional steroid injection and the conventional fully-covered metal stent. The lumen-apposing metal stent (LAMS) exhibit lumen-apposing and dual anchoring capabilities. While it has primarily been used to drain pancreatic fluid collections, LAMS may serve as a more effective alternative to standard endoscopic therapies for benign strictures.

Research frontiers

Currently, there are two recent retrospective studies in the literature that describe use of LAMS for benign strictures. Irani and colleagues found that in a group of 25 patients, the placement of AXIOS™ stent led to resolution of symptoms at 6 mo in 60.0% of cases. Yang and colleagues found that in a group of 30 patients, the placement AXIOS™ stent led to resolution of symptoms in 90.0% of cases, and 82.6% continued to have improved symptoms after LAMS removal. The migration rates in the Irani *et al* and Yang *et al* are 7.0% and 8.0%, respectively. Currently there have been no prospective studies using LAMS and this may be worthwhile in the future to truly determine the ideal clinical scenarios when LAMS should be used.

Innovations and breakthroughs

In the authors' group of 21 cases, short-term clinical success was achieved in 90.5% of cases, and long-term clinical success was achieved 66.7% of cases. We also report the outcomes of 16 mm × 30 mm NAGI™ stent that was successfully placed in 3 cases. The migration rate for those who underwent LAMS placement was 19.0%, which appears to be higher than other studies on this topic. Furthermore, in contrast to prior reports, the authors found complications of LAMS placement not described in prior reports. These primarily include angulation and stricture overgrowth, which played significant roles in preventing clinical success in the cases.

Applications

The authors found that the utilization of LAMS is technically feasible and safe as a primary or salvage therapy for benign GI strictures with a high short-term clinical success rate. However, the adverse events as described above highlight the need for further study in this area to better understand which patients and

which strictures are most optimal for management with LAMS. Uncovering this information will contribute towards the potential widespread adoption of this technique for the treatment of benign GI strictures.

Terminology

Covered self-expandable metal stent: This stent has been widely used in malignant obstruction. The presence of a covering membrane allows the lumen to remain patent despite structured tissue overgrowth. Furthermore, it prevents the metal wires from burrowing into the wall, which allows for easier retrieval; LAMS: This newer stent has been widely used for drainage of pancreatic fluid collections. It exhibits lumen-apposing and dual anchoring capabilities. The anchoring flanges are thought to lower the risk of stent migration.

Peer-review

An International Multicenter study that is clinically meaningful. It is a retrospective analysis of LAMS placement in three tertiary care hospitals that add value to the knowledge of benign stricture treatment.

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CASE REPORT

Retroperitoneal epithelioid sarcoma: A case report

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Abstract

Epithelioid sarcoma (ES), a mesenchymatous malign neoformation, is often diagnosed in later stages and associated with high recurrence index, metastasis and mortality. We report a case of a 65 years old male, with history of abdominal pain and upper gastrointestinal bleeding. Endoscopy demonstrated a posterior duodenal wall perforation communicating with a solid retroperitoneal neoformation. Endoscopic biopsy was performed, with a final report of ES. The patient was submitted for surgical palliation due to the tumor's unresectability. Retroperitoneal ES is an extremely rare condition with limited reports in the literature where guidelines for its optimal treatment are not well established.

Key words: Epithelioid sarcoma; Retroperitoneal; Mesenchymatous neoformation; Duodenal perforation; Endoscopy

Core tip: Epithelioid sarcoma (ES) is a rare malign neoformation, often diagnosed in later stages and associated with high recurrence index and mortality. We report a case of a 65 years old male with a posterior duodenal wall perforation found during endoscopy, communicating with a solid retroperitoneal neoformation. Endoscopic biopsies were sufficient for the diagnosis. Retroperitoneal ES is an extremely rare condition with limited reports, where guidelines for its optimal treatment are not well established.

Coronado JA, Chávez MA, Manrique MA, Cerna J, Trejo AL. Retroperitoneal epithelioid sarcoma: A case report. *World J*

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INTRODUCTION

Epithelioid sarcoma (ES) was originally described in 1970 by Enzinger[1]. It is a rare malignant mesenchymatous tumor more frequently found in young patients from 23 to 40 years old; however with a range of presentation between 4 and 90 years of age[2]. Due to its diverse clinical scenario, diagnosis is generally delayed. Usually divided in proximal and distal presentation, with predominant topography on distal zones such as upper extremities, mainly fingers, hands and wrists[3]. The distal form is composed of spindle to polygonal epithelioid cells arranged in nodules with central necrosis. The proximal form was described in 1997, arising in the deep part of the pelvis, perineum and genital tract. It presents large epithelioid carcinoma-like cells and has a more aggressive clinical course than the distal presentation[4].

Microscopic appearance of ES ranges from spindle cells to large polygonal cells with an acidophilic cytoplasm[5]. Diagnosis can be confirmed with immunochemical staining positive for epithelial markers such as cytokeratin and epithelial membrane antigen, a mesenchymatous marker (vimentin) and CD34[6]. Finally, in some small series cytogenetic analysis has been performed, finding genetic alterations at the long arm of chromosome 22[7].

ES is distinguished by its high recurrence rate, with local recurrences reported in up to 77%, and an elevated percentage of node and lung metastasis (36%-44%)[8]. Five year, and 10-year survival are 65.3% and from 25% to 50% respectively[6]. However, the mean time from recurrence to death in patients older than 36 years stands at 5.6 ± 4.5 mo and in younger patients at 15.2 ± 17.2 mo[3]. Furthermore, the specific treatment for this pathology has not been established by international consensus; where a distal type ES tends to avoid amputation, a local recurrence is treated with local excision plus radiotherapy[7]. But, in tumors with unfavorable factors such as, proximal type or size greater than 5 cm, a systemic treatment plus surgical intervention should be evaluated[9].

CASE REPORT

A 65 years old Hispanic male with a remarkable medical history, presented with a one month history of right upper quadrant abdominal pain and upper gastrointestinal bleeding characterized by intermittent melena. Episodes of fever were also reported. Physical examination revealed a palpable right upper quadrant abdominal mass extending up to 4 cm below the costal margin. CT scan reported an infiltrative lesion in duodenum and gallbladder affecting the splenic, hepatic and mesenteric vascularity (Figures 1 and 2). Endoscopy was performed finding a 2 cm opening from the posterior duodenal wall communicating with a solid retroperitoneal mass, irregular, indurated and extremely friable measuring more than 10 cm in diameter (Figure 3).

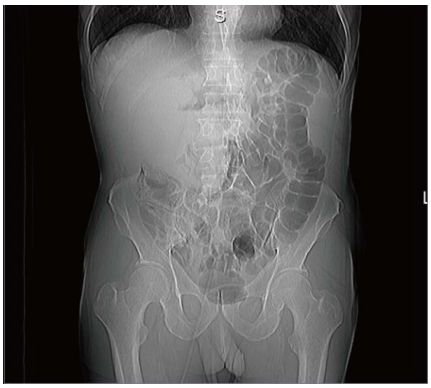

Figure 1 Abdominal radiography showing right upper quadrant mass enlargement.

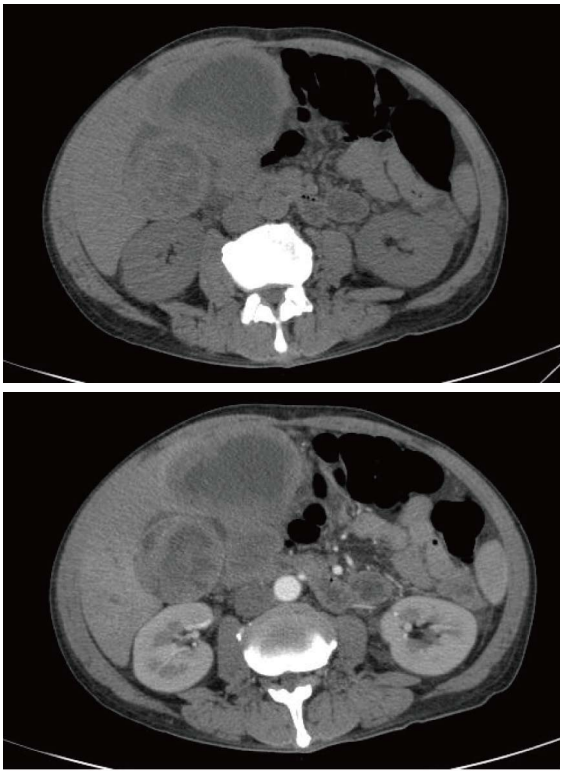

Figure 2 Computed tomography scan (simple and arterial phase) with infiltrative lesion at duodenum and gallbladder.

The patient was treated with palliative surgery, performing a gastro-jejunal anastomosis, with a postoperative report of retroperitoneal tumor invading duodenum and gallbladder. Final histopathological report stated the presence of retroperitoneal ES positive for cytokeratin and vimentin (Figure 4). Lastly, the patient was deceased two weeks after the initial diagnosis.

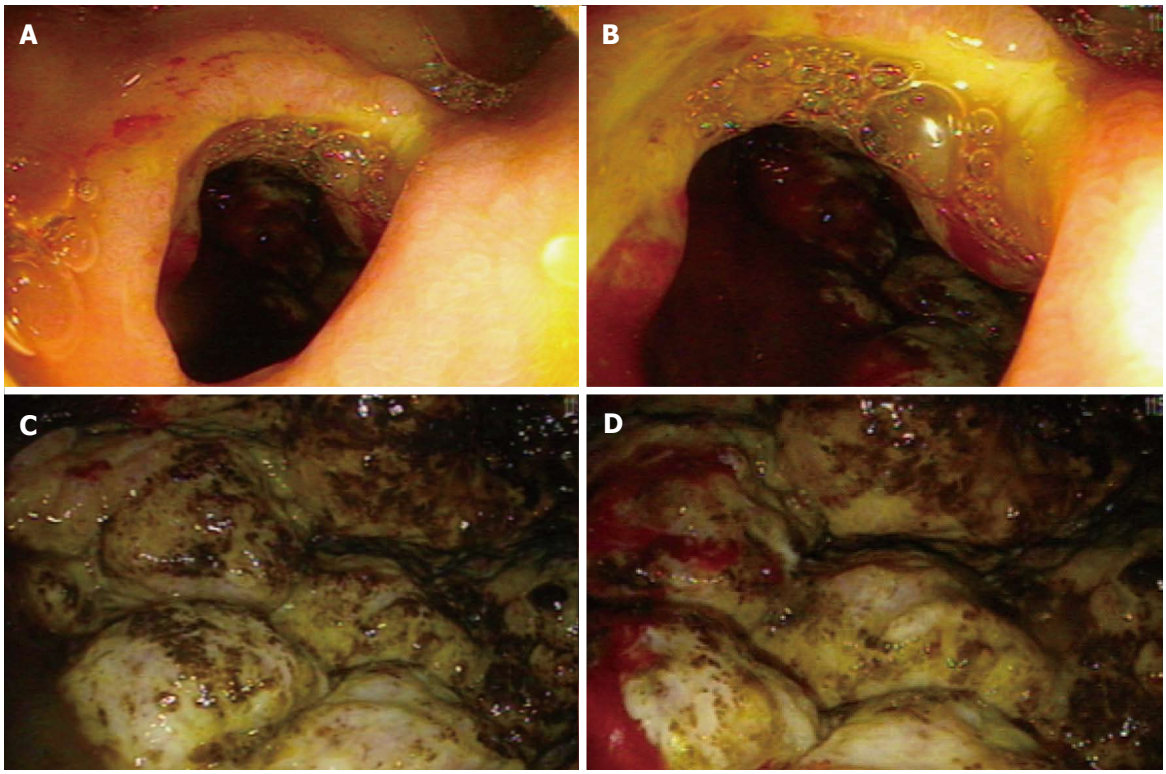

Figure 3 Duodenal posterior wall perforation (A and B), retroperitoneal solid and irregular neoplasia (C), extreme friability and spontaneous bleeding (D).

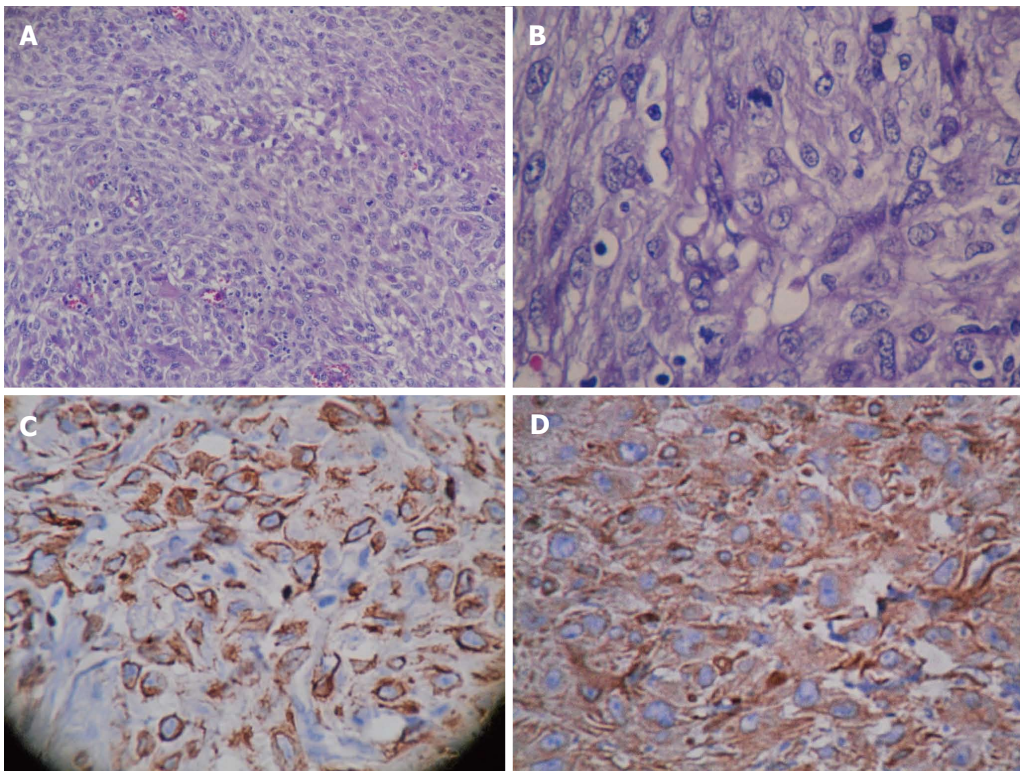

Figure 4 H and E with fusiform and giant pleomorphic cells, increased mitosis (A and B), positive staining for vimentin and cytokeratin respectively (C and D).

DISCUSSION

ES is a soft tissue malignant entity with a high recurrence rate and mortality. Thus, the importance of reporting this case in order to increase awareness of this rare disease; since it seems only an early diagnosis with

definite surgical treatment can improve prognosis. In this particular case, endoscopy was helpful as the duodenal perforation allowed direct examination and prompt biopsy samples from the lesion. However, urgent surgical consultation was needed once the bowel perforation was found. In conclusion, ES is an infrequent variant of malignant sarcoma, with a very aggressive behavior, and which will only benefit with a prompt diagnosis and intensive multidisciplinary treatment.

COMMENTS

Case characteristics
A 65 years old Hispanic male with right upper quadrant abdominal pain and upper gastrointestinal bleeding characterized by intermittent melena.

Clinical diagnosis
Palpable right upper quadrant abdominal mass extending up to 4 cm below the costal margin.

Differential diagnosis
Primary neoplasm arising from a retroperitoneal structure (pancreas, adrenal glands, kidneys and duodenum), lymphoma.

Laboratory diagnosis
All labs were within normal limits except for chronic moderate anemia.

Imaging diagnosis
CT scan showed an infiltrative lesion in duodenum and gallbladder affecting the splenic, hepatic and mesenteric vascularity.

Endoscopy
Endoscopy showed a 2 cm opening from the posterior duodenal wall communicating with a solid retroperitoneal mass, irregular, indurated and extremely friable measuring more than 10 cm in diameter.

Pathological diagnosis
Retroperitoneal epithelioid sarcoma (ES) positive for cytokeratin and vimentin.

Treatment
Palliative surgery, a gastro-jejunal anastomosis.

Related reports
Epitheliod sarcoma is a malign entity with distal and proximal forms. The proximal form arising in the deep part of the pelvis, perineum and genital tract or retroperitoneum has been very rarely reported.

Term explanation
ES is a rare malignant mesenchymatous tumor more frequently found in young patients from 23 to 40 years old. Usually divided in proximal and distal presentation, with predominant topography on distal zones such as upper extremities, mainly fingers, hands and wrists. The proximal form originates in the deep part of the pelvis, perineum and genital tract. It presents large epithelioid carcinoma-like cells and has a more aggressive clinical course than the distal presentation.

Experiences and lessons
Retroperitonal ES is an extremely rare pathology, the duodenal perforation allowed the passage of a videoendoscope providing a very unusual and direct endoscopic view of the neoformation.

Peer-review
The authors describe a rare and an interesting case of ES.

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CASE REPORT

Endoscopic ultrasound-guided fine-needle aspiration for diagnosing a rare extraluminal duodenal gastrointestinal tumor

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Abstract

Duodenal gastrointestinal stromal tumors (GISTs) are extremely rare disease entities, and the extraluminal type is difficult to diagnose. These tumors have been misdiagnosed as pancreatic tumors; hence, pancreaticoduodenectomy has been performed, although partial duodenectomy can be

performed if accurately diagnosed. Developing a diagnostic methodology including endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) has allowed us to diagnose the tumor directly through the duodenum. Here, we present a case of a 50-year-old woman with a 27-mm diameter tumor in the pancreatic uncus on computed tomography scan. EUS showed a well-defined hypoechoic mass in the pancreatic uncus that connected to the duodenal proper muscular layer and was followed by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Histological examination showed spindle-shaped tumor cells positively stained for *c-kit*. Based on these findings, the tumor was finally diagnosed as a duodenal GIST of the extraluminal type, and the patient underwent successful mass resection with partial resection of the duodenum. This case suggests that EUS and EUS-FNA are effective for diagnosing the extraluminal type of duodenal GISTs, which is difficult to differentiate from pancreatic head tumor, and for performing the correct surgical procedure.

Key words: Gastrointestinal stromal tumor; Duodenum; Extraluminal type; Pancreatic head tumor; Endoscopic ultrasonography; Endoscopic ultrasound-guided fine-needle aspiration; Partial resection

Core tip: Duodenal gastrointestinal stromal tumors are extremely rare disease entities, and the extraluminal type is difficult to diagnose. Therefore, these tumors have been misdiagnosed as pancreatic tumors; hence, pancreaticoduodenectomy has been performed, although partial duodenectomy can be performed if accurately diagnosed. Recent advances in developing endoscopic ultrasonography and endoscopic ultrasound-guided fine-needle aspiration are helpful for accurate diagnosis of the tumors located in the area and effective for performing the correct surgical procedure.

Hayashi K, Kamimura K, Hosaka K, Ikarashi S, Kohisa J, Takahashi K, Tominaga K, Mizuno K, Hashimoto S, Yokoyama J, Yamagiwa S, Takizawa K, Wakai T, Umezu H, Terai S. Endoscopic ultrasound-guided fine-needle aspiration for diagnosing a rare extraluminal duodenal gastrointestinal tumor. *World J Gastrointest Endosc* 2017; 9(12): 583-589 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i12/583.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i12.583

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a group of mesenchymal tumors in the gastrointestinal tract that arise from the interstitial cells of Cajal[1]. These tumors contribute to about 1%-3% of all gastrointestinal malignancies and are frequently found in the stomach (60%-70%). Duodenal GISTs are very rare, with 5% rate of occurrence[2]. They are thought to be caused by a mutation in the *c-kit* gene and alpha-type platelet-derived growth factor receptor gene in the intestinal cells of Cajal or their precursors[3]. Due to its rarity and the complex anatomy of the pancreaticoduodenal region, it is extremely difficult to differentially diagnose duodenal GISTs from pancreatic tumors, especially when it is extraluminal. Because misdiagnosis may lead to an inaccurate choice of surgical procedure, we report our case of extraluminal-type duodenal GISTs correctly diagnosed with endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) followed by successful resection of the tumor. To date, the usefulness of these modalities in diagnosing the tumor has not been reported. This case suggests that EUS and EUS-FNA are effective for diagnosing extraluminal type of duodenal GISTs and for performing the correct surgical procedure.

CASE REPORT

A 50-year-old Japanese woman was found to have a pancreatic head tumor by abdominal ultrasonography on a health checkup and was referred to our hospital for further examination. She was in good physical condition, no evidence of melena, and had no remarkable history. The results of her initial physical examination were as follows: Body temperature, 37.0 ℃ blood pressure, 127/78 mmHg; pulse rate, 74 bpm, regular; a flat and soft abdomen without pain or tenderness; and no palpable masses.

Blood tests performed on admission revealed a slight elevated inflammatory response with a white blood cell count of 11370/μL and C-reactive protein level of 0.33 mg/dL. Other laboratory findings were normal including a red blood cell count of 326 × 10^4/μL and hemoglobin of 13.7 g/dL, indicating no existence of anemia. Tumor markers including carbohydrate antigen 19-9, carcinoembryonic antigen, DUPAN, SPan-1, and soluble interleukin-2 receptor levels were within normal limits.

An abdominal dynamic contrast-enhanced computed tomography (CT) showed a 27-mm diameter tumor in the pancreatic uncus, which was well defined and enhanced starting from the arterial to the venous phase, exhibiting the greatest enhancement in the arterial phase (Figure 1). Magnetic resonance imaging revealed the mass to be hypointense on T1-weighed imaging and slightly hyperintense on T2-weighed imaging. The contrast enhancement study showed a similar pattern on CT suggesting the diagnosis of duodenal GIST or pancreatic head neuroendocrine tumor (NET). Therefore, endoscopic examination was performed for the further diagnosis.

Upper gastroendoscopy showed a slightly elevated lesion located in the inferior angle of the duodenum with normal overlying mucosa detected on upper gastrointestinal endoscopy (Figure 2). EUS showed a well-defined hypoechoic mass placed close to the

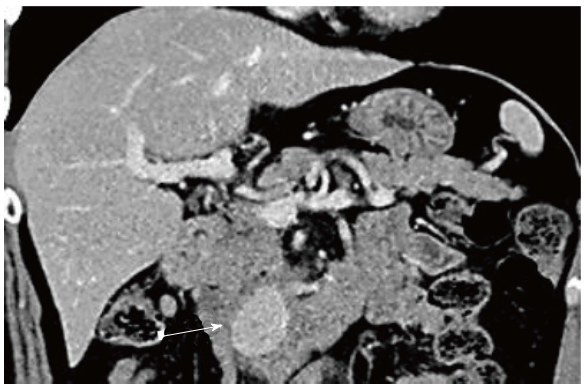

Figure 1 Abdominal dynamic contrast-enhanced computed tomography showed a 27-mm diameter tumor in the pancreatic uncus, which was well defined and enhanced from the arterial phase, exhibiting the greatest enhancement in the arterial phase. White arrow indicates the tumor.

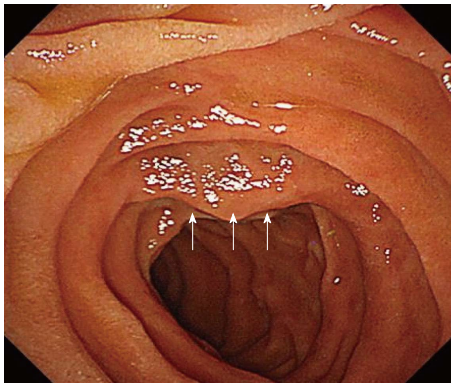

Figure 2 A slightly elevated lesion located in the inferior angle of the duodenum with normal overlying mucosa was detected on upper gastrointestinal endoscopy. White arrows indicate the elevation.

pancreatic uncus; however, the tumor was clearly revealed to be connected to the muscularis propria layer of the duodenum (Figure 3). Based on the EUS findings, duodenal GIST or pancreatic NET was suspected and EUS-FNA was performed for a definitive diagnosis. Histological examination revealed that the tumor was mainly composed of spindle-shaped cells (Figure 4). Immunohistochemistry (IHC) showed that the tumor cells were positive for c-kit, CD34, and S-100, but negative for desmin (Figure 4). Based on these results, the tumor was diagnosed as the extraluminal type of duodenal GIST.

The patient underwent mass resection of the tumor with partial resection of the second part of the duodenum. The tumor showed extraluminal growth and protruded into the pancreas but did not infiltrate the pancreatic parenchyma, consistent with the EUS findings. In addition, there was no ascites and no peritoneal dissemination.

Histopathology of the resected tumor showed a mesenchymal, sharply margined tumor of 30 mm × 22 mm × 22 mm size, consisting of spindle cells without necrosis. Mitosis was detected in 2/50 high-power fields

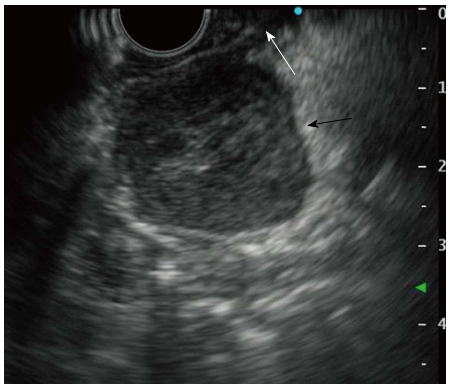

Figure 3 Endoscopic ultrasonography showed a well-defined hypoechoic mass in the pancreatic uncus, and the tumor connected with the muscularis propria layer of the duodenum. Black arrow indicates the tumor and white arrow indicates the muscularis propria layer.

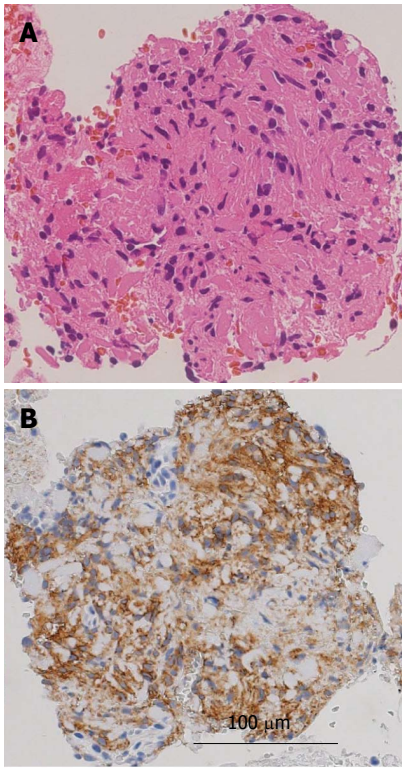

Figure 4 Histological analysis of specimen collected by endoscopic ultrasound-guided fine-needle aspiration. A: Hematoxylin and eosin staining revealed that the tumor was mainly composed of spindle-shaped cells; B: The tumor cells were positive for *c-kit*.

(HPFs). The tumor cells were positive for c-kit, and MIB-1 labeling index (Ki-67 stain) was < 1% (Figure 5).

No postoperative recurrence has been observed to date, and the patient did not require adjuvant chemotherapy for 2 years.

DISCUSSION

GISTs are the most common mesenchymal tumors in the gastrointestinal tract, contributing about 1%-3% of all gastrointestinal malignancies[1]. GISTs develop most

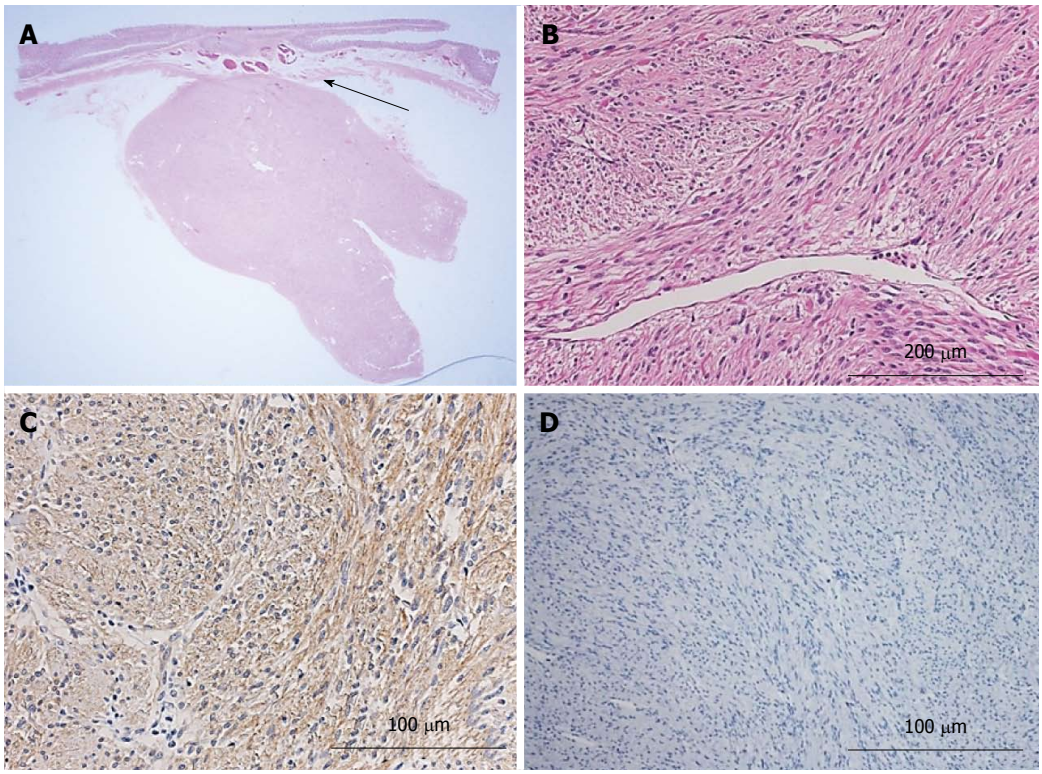

Figure 5 Histological analysis of resected tumor tissue. A: Macroscopic finding showed 30 mm × 22 mm × 22 mm sized tumor showing extraluminal growth from duodenum (black arrow); B: Hematoxylin and eosin-stained sections showed that the tumor was mainly composed of spindle-shaped cells without necrosis; C: The tumor cells appeared immunohistochemically positive for *c-kit*; D: Mitosis was detected in 2/50 high-power fields, and MIB-1 labeling index (Ki-67 stain) was < 1%.

frequently in the stomach (60%-70%), followed by the jejunum and ileum (20%-25%), duodenum (5%), colon and rectum (5%), and esophagus (< 5%)[3]. Miettinen *et al*[4] reported that duodenal GISTs most frequently involved the second portion of the duodenum, followed by the third, fourth, and first portions. They also reported that a majority of duodenal GISTs show submucosal tumor with a centrally ulcerated umbilication[4]; therefore, duodenal GISTs present with gastrointestinal bleeding, epigastric pain, a palpable mass, and intestinal obstruction[4].

In our case, the tumor exhibited exclusive extraluminal growth into the pancreatic head, and there was a slightly elevated lesion without ulceration in the inferior angle of the duodenum; this atypical finding made it difficult to distinguish it from a pancreatic NET[5]. Because the lesion without ulceration is difficult to diagnose by forcep-based biopsy on normal mucosa[6], EUS and EUS-FNA are helpful for its diagnosis. For EUS, it is important to determine whether there is a connection with gastrointestinal wall because it is the most accurate test to distinguish the layer where a lesion is located. The accuracy of the diagnosis was < 50% when using only EUS[7]. The sensitivity of EUS-FNA cytology was 84.4% for GISTs located in the stomach but poor for lesions located in the duodenum[8]. Table 1 summarizes the cases of duodenal gastrointestinal tumors diagnosed with endoscopic ultrasound-guided fine-needle aspiration. Only a few reports show the usefulness of EUS-FNA for the diagnosis of duodenal GIST, especially when it is extraluminal type. Based on Skandalakis classification, among 11 cases reported, only 3 cases were extraluminal type and 2 showed mixed type. Ueda *et al*[9] reported that they diagnosed intra- and extraluminal growth type duodenal GIST by EUS-FNA. As summarized, while all case showed somewhat level of submucosal elevation, no ulcer was complicated in the lesion and EUS showed clear hypoechoic mass in nine cases among 11 cases (Table 1). In addition, the connection to the proper muscle layer was shown in nine cases and FNA tissues have successfully performed to determine the histological analyses.

In the reported case, EUS revealed the connection of the tumor and the muscularis propria layer (the fourth EUS layer). EUS-FNA showed that the tumor was composed of spindle-shaped cells, which were positive for c-kit, CD34, and S-100, but not for desmin, reported as a typical IHC result of GIST[10]. An accurate diagnosis helped determine the surgical procedure. Therefore, our case was successfully treated as reported[11].

Prognostic factors are very important for both assessing recurrence risk and the choice of adjuvant and neoadjuvant therapy[12]. The recently proposed "modified National Institutes of Health (NIH) classification" is defined by four factors: Number, size, location, and rupture of mitoses. This classification may offer advantages in the selection of patients who may require adjuvant therapy[13]. All GISTs that occurred in

Table 1 Summary of cases of duodenal gastrointestinal tumors diagnosed with endoscopic ultrasound-guided fine-needle aspiration

Ref.	Age (yr)	Gender	Location in duodenum	Size (mm)	Endoscopic findings			EUS findings				Immunohistochemistry				Skandalakis classification	Treatment	Adjuvant chemo-therapy	Clinical course	Follow up period (yr)
					SMT	Central depression	Ulcerative lesion	well-demar-cated	Internal echogram	Cystic change	Connected to proper muscles	CD117	CD34	S-100	MIB-1 labeling index					
9	72	F	3rd	26	+	-	-	+	hypo	-	+	+	+	N.A.	< 1%	Mixed	Partial duodenectomy	-	No recurrence	N.A.
16	62	F	2nd	40	+	-	-	+	hypo	-	+	+	+	-	0.60%	Eodoluminal	Partial duodenectomy	-	No recurrence	6
16	69	M	1st	15	+	+	-	+	iso	-	+	+	+	N.A.	0.50%	Eodoluminal	No surgery, Follow up	-	SD	5
16	76	M	2nd	35	+	+	-	-	hetero	+	+	+	-	-	0.70%	Eodoluminal	No surgery, Follow up	-	SD	3
17	50s	F	2nd	35	+	-	-	+	N.A.	-	N.A.	+	±	+	< 5%	NA	Partial duodenectomy	-	N.A.	NA
18	85	F	2nd	30	+	-	-	+	hypo	-	+	+	±	-	N.A.	Eodoluminal	No surgery, Follow up	-	SD	1.6
19	50s	F	3rd	25	+	+	-	+	hypo	-	+	+	+	-	2%	Eodoluminal	Partial duodenectomy	-	No recurrence	1.3
19	30s	M	3rd	20	±	-	-	+	Aypo	-	+	+	+	-	3%	Extraluminal	Partial duodenectomy	-	No recurrence	1.2
20	75	M	3rd	60	+	-	-	+	hypo	-	-	+	-	-	2%	Extraluminal	Subtotal stomach-preserving Pancreaticoduodenectomy	+	No recurrence	1
21	51	M	2nd	27.5	+	-	-	+	hypo	-	+	+	+	N.A.	N.A.	Mixed	Surgery (no detail available)	N.A.	N.A.	N.A.
Our case	50	F	2nd	30	±	-	-	+	hypo	-	+	+	-	-	< 1%	Extraluminal	Partial duodenectomy	-	No recurrence	2

EUS: Endoscopic ultrasound; ALT: Alanine aminotransferase.

the intestines had more than a moderate possibility of metastasis when they were > 5 cm or had > 5 mitoses/50 HPFs. In tumors < 5 cm with a mitotic count < 5/50 HPFs, the intestinal GISTs had a low probability of metastasis[14].

Patients with duodenal GISTs classified as intermediate or high risk for tumor relapse should be treated with 400 mg imatinib daily for 3 years and there is no benefit for patients classified at low risk. As summarized in Table 1, other than 2 cases with no follow up data are available after the surgical treatment, no recurrence after the surgical treatment was confirmed in all other 6 cases for whom the surgery was performed. While other 3 cases showed stable disease with no surgical treatment because of low risk. Our patient was low risk according to the NIH consensus criteria for risk satisfaction of GISTs and has been followed without adjuvant chemotherapy.

After completed tumor resection, follow-up care should be every 3-6 mo, including clinical examination and CT scans of the abdomen and pelvis once a year for 5 years[15]. Our patient has been doing well with no tumor recurrence for 2 years since her surgery and will continue strict CT follow-up.

In summary, we have described a rare extraluminal growth type of duodenal GIST and showed the usefulness of EUS-FNA. This report will aid physicians in diagnosing rare duodenal tumors and contribute to determining the appropriate therapeutic strategy.

COMMENTS

Case characteristics

The authors present a case of a 50-year-old woman with a 27-mm diameter tumor in the pancreatic uncus on computed tomography scan. Endoscopic ultrasound (EUS) showed a well-defined hypoechoic mass in the pancreatic uncus that connected to the duodenal proper muscular layer and was followed by EUS-guided fine-needle aspiration (EUS-FNA). Histological analysis showed spindle-shaped tumor cells positively stained for c-kit. Therefore, the tumor was diagnosed as a duodenal gastrointestinal stromal tumors (GISTs) of the extraluminal type, and the patient underwent successful mass resection with partial resection of the duodenum.

Clinical diagnosis
A mass in the pancreatic uncus that connected to the duodenal proper muscular layer.

Differential diagnosis
Pancreatic cancer; gastrointestinal stromal tumors; neuroendocrine tumor.

Laboratory diagnosis
Laboratory data showed a slight elevated inflammatory response with a white blood cell count of 11370/μL and C-reactive protein level of 0.33 mg/dL. Tumor markers including carbohydrate antigen 19-9, carcinoembryonic antigen, DUPAN, SPan-1, and soluble interleukin-2 receptor levels were within normal limits.

Imaging diagnosis
EUS showed a well-defined hypoechoic mass in the pancreatic uncus that connected to the duodenal proper muscular layer. Magnetic resonance imaging revealed the mass to be hypointense on T1-weighed imaging and slightly hyperintense on T2-weighed imaging. The imaging studies suggested the diagnosis of duodenal GIST or pancreatic head neuroendocrine tumor (NET).

Pathological diagnosis
IHC showed that the tumor cells were positive for c-kit, CD34, and S-100, but negative for desmin. Based on these results, the tumor was diagnosed as the extraluminal type of duodenal GIST.

Treatment
The patient underwent successful mass resection with partial resection of the duodenum.

Term explanation
GISTs: Gastrointestinal stromal tumors; NET: Neuroendocrine tumor; EUS: Endoscopic ultrasonography; FNA: Fine-needle aspiration.

Experiences and lessons
This case suggests that EUS and EUS-FNA are effective for diagnosing the extraluminal type of duodenal GISTs, which is difficult to differentiate from pancreatic head tumor, and for performing the correct surgical procedure.

Peer-review
This is a well written case.

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CASE REPORT

Deanxit relieves symptoms in a patient with jackhammer esophagus: A case report

Jin-Ying Li, Wen-Huan Zhang, Chun-Ling Huang, Dang Huang, Guo-Wen Zuo, Lie-Xin Liang

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Author contributions: Zuo GW designed the report; Li JY collected references and prepared the manuscript, with the help of Huang D; Zhang WH and Huang CL provided the figures; Zuo GW and Liang LX supervised the preparation of the manuscript.

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Abstract

Jackhammer (hypercontractile) esophagus presents with dysphagia and chest pain. Current treatments are limited. We describe a 60-year-old man who presented with dysphagia, chest pain and heartburn for a period of 1 year. His workup showed Barrett's esophagus on endoscopy and high-resolution manometry demonstrated jackhammer esophagus with esophagogastric junction outflow obstruction. The patient was treated with proton pump inhibitor and nifedipine but without resolution of his symptoms. He was followed up to assess the efficacy of treatment with deanxit (flupentixol + melitracen). Dysphagia and chest pain resolved during the therapeutic trial and efficacy was maintained on maintenance treatment without troublesome side effects.

Key words: High-resolution manometry; jackhammer esophagus; Deanxit; Therapy

Core tip: Low-dose antidepressants can improve patients' reaction to the pain associated with esophageal dynamic disorders. The case report describes that deanxit (flupentixol + melitracen) has a positive effect on a new, rare disease, jackhammer esophagus, and speculates upon the potential relationship between mental factors and jackhammer esophagus.

Li JY, Zhang WH, Huang CL, Huang D, Zuo GW, Liang LX. Deanxit relieves symptoms in a patient with jackhammer esophagus: A case report. *World J Gastrointest Endosc* 2017; 9(12):

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INTRODUCTION

High-resolution manometry (HRM) has provided a new method for clinical diagnosis and treatment of esophageal motility disorders. Based on HRM techniques, the new Chicago classification has revised the esophageal motility disorder diagnostic criteria, mainly for achalasia and esophageal body motility disorders. Jackhammer esophagus is a new entity within spastic disorders of the esophagus[1]. Moreover, it has recently been described by a new Chicago Classification version 3.0 with at least two swallows with distal contractile integral (DCI) > 8000 mmHg-s-cm[2]. We describe a patient with impaired esophagogastric junction (EGJ) relaxation and hypercontractile peristaltic disorder, accompanying depressive disorder, which has not been reported in China. Treatment with deanxit (flupentixol + melitracen) led to an unusual recovery.

CASE REPORT

A 60-year-old man visited our hospital because of a 1-year history of intermittent and recurrent episodes of dysphagia, chest pain and heartburn in January 2015. In another hospital, he had taken proton pump inhibitors (PPIs) for > 1 mo, but he was not relieved of any symptoms. There was nothing remarkable in his medical history. Physical and laboratory examinations showed no specific findings. Endoscopy showed possible Barrett's esophagus (BE) (Figure 1A). Moreover, esophageal mucosal biopsy suggested gastric mucosa ectopia. A barium esophagogram showed reflux esophagitis and spastic contraction in the distal esophagus (Figure 1B). He underwent HRM (Sierra Scientific Instruments, Los Angeles, CA, United States) and 24-h esophageal impedance-pH monitoring (Sierra Scientific Instruments). HRM showed that the maximum DCI was 8099.9 mmHg-s-cm and the integrated relaxation pressure (IRP) was 21.5 mmHg (Figure 1C). Pathological acid reflux was reported by 24-h esophageal impedance-pH evaluation (Figure 1D). Medical therapy with nifedipine 10 mg twice daily, esomeprazole 20 mg twice daily and teprenone 50 mg twice daily for approximately 10 mo showed no improvement in dysphagia and chest pain, but the symptoms of acid regurgitation and heartburn had relieved.

He was seen in our hospital in December 2015 with worsening dysphagia and chest pain. However, laboratory investigations were normal again including serum troponin level, electrocardiography monitoring and coronary angiography. HRM and 24-h esophageal impedance-pH monitoring were repeated. HRM showed typical hypercontractile contractions (6 swallows with DCI > 8000 mmHg-s-cm in 10 liquid swallows) and IRP 14.7 mmHg (Figure 2A), whereas impedance-pH monitoring was negative (Figure 2B). Close examination of his medical history revealed long-term sleep disorders, with difficulty falling asleep, worrying about cancer, and anxiety. The patient was judged to be in a depressive state by a psychiatrist. Drug therapy was adjusted to deanxit 0.5 mg/10 mg (one piece) twice daily, rabeprazole 10 mg twice daily and hydrotalcite 1 g three times daily, and the patient's symptoms improved, with no obviously reflux, chest pain, and dysphagia after 5 d treatment. Moreover, he continued this therapy as-maintained basis.

At follow-up 5 mo later, the patient described clinical improvement with only one episode of dysphagia and chest pain, because of stopping his medication without permission. However, symptoms were relieved soon after he takes medicine. He was re-examined by HRM in May 2016, which showed IRP 10.1 mmHg (normal < 15 mmHg) and mean DCI 6750 mmHg-s-cm (Figure 3). The total period of treatment was 6 mo, with deanxit dose gradually reduced until withdrawal under the guidance of a psychologist and gastroenterologist. In June 2017, the patient had recovered well without recurrence of symptoms.

DISCUSSION

Jackhammer esophagus is a rare disorder that occurs in 4% of patients referred to a tertiary center for HRM, and these patients with extreme phenotypes of esophageal hypercontractility present mainly with dysphagia, chest pain, and gastroesophageal reflux symptoms[3]. Nowadays there appears to be no clear consensus about optimal therapy, and options are similar to other esophageal dysmotility disorders. Pharmacological treatment should be considered first, with a combination of nitrates, calcium channel blockers, phosphodiesterase-5 inhibitors and PPIs having potential benefit[4]. Recently, Marjoux *et al*[5] reported that esophageal botulinum toxin was effective for treatment of hypertensive esophageal motility disorders. There were also recently reported cases of successful treatment with peroral endoscopic myotomy[6] and balloon dilatation[7]. Tsutomu *et al*[8] have reported that surgery using thoracoscopic esophageal extended myotomy is beneficial.

Patients with jackhammer esophagus can present with mechanical EGJ outflow obstruction, gastroesophageal reflux disease, or primary esophageal muscle hypercontractility[3]. Our patient had high IRP; a hypercontractile peristaltic disorder of the esophagus that overlaps with BE. The first treatment strategy of spastic disorders depends on whether there is an accompanying EGJ outflow obstruction[4]. Moreover, there is a lack of evidence for the value of pharmacological treatment alone if EGJ relaxation is impaired. Therefore, we selected medical therapy first. A trial of nifedipine and PPIs have been chosen. The IRP was normal and changed to jackhammer esophagus without EGJ outflow obstruction and pathological acid reflux.

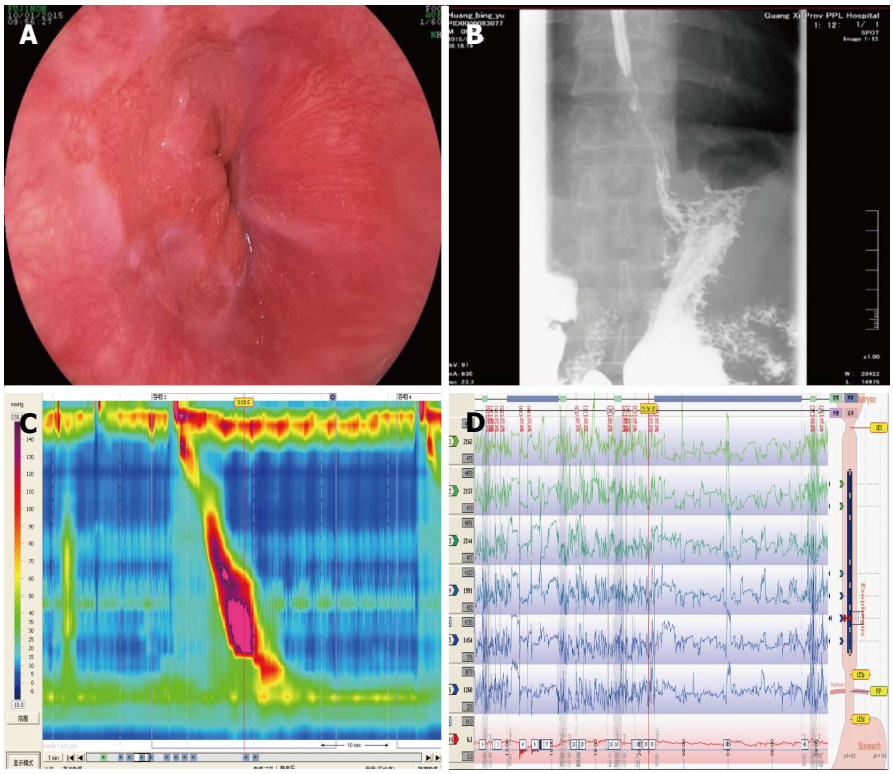

Figure 1 The workup of the patient for the first time. A: Esophageal lesions of the patient under endoscopy, which were suggestive of BE; B: Barium esophagogram showing reflux esophagitis and spastic contraction in the distal esophagus; C: Representative swallow from the patient's initial HRM. The median IRP was high at 21.5 mmHg, and the DCI was elevated to 8099.9 mmHg-s-cm; D: 24-h pH-impedance monitoring. It can monitor 100% acid reflux into the esophagus. DCI: Distal contractile integral; HRM: High-resolution manometry; IRP: Integrated relaxation pressure.

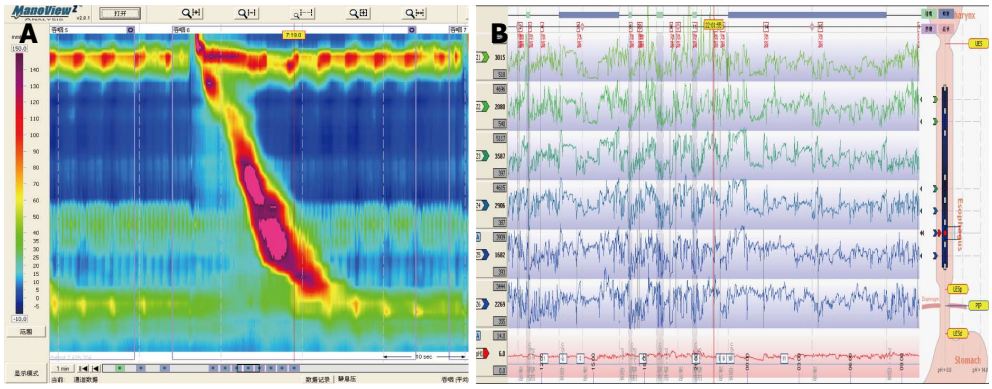

Figure 2 Esophageal test results for the second time. A: Representative swallow from the patient's repeat esophageal HRM. Median IRP was normal at 14.7 mmHg. DCI was higher than normal, which was 8120.1 mmHg-cm-s, and six swallows with DCI > 8000 mmHg-s-cm in 10 liquid swallows. Esophageal manometry was consistent with jackhammer esophagus; B: 24-h pH-impedance monitoring was repeated, which was negative for gastroesophageal reflux disease. DCI: Distal contractile integral; HRM: High-resolution manometry; IRP: Integrated relaxation pressure.

Low-dose antidepressants can improve patients' reaction to pain without objectively improving motility function[9]. Our patient had obvious chest pain and dysphagia with esophageal hypercontractility. We allowed him to take antidepressants (deanxit) because he had depression. The patient's clinical and objective esophageal indexes were improved. Previous studies have established that the psychosocial aspects are related to gastroesophageal reflux disease and functional esophageal disorders, such as functional chest pain, functional dysphagia and hypersensitive esophagus[10,11]. In the present study, we examined the influence of the relationship between mental factors and jackhammer esophagus. Deanxit had surprising efficacy for this patient, so we speculated that his depressive disorder may have caused hypercontractile peristaltic disorder because of nonspecific esophageal motility disorder. Alternatively, it may be that the patient endured painful symptoms for a long period, resulting in psychiatric comorbidity of jackhammer esophagus. The underlying pathological mechanisms in this case are unclear and deserve further study.

In summary, despite the evidence of efficacy, the long-term optimal management of jackhammer esophagus is

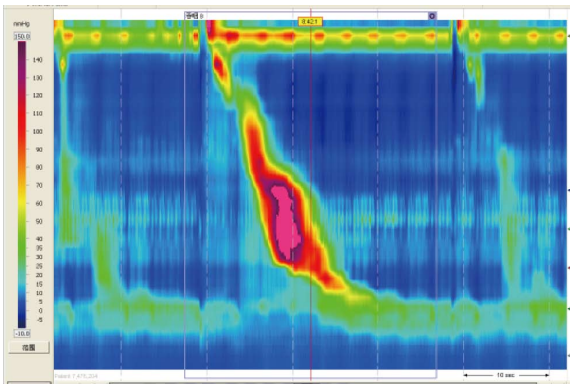

Figure 3 A representative swallow from the patient's repeat esophageal high-resolution manometry after administration of deanxit. Median IRP was elevated at 10.1 mmHg. DCI of each swallow was higher than the normal range but < 8000 mmHg-cm-s, which was improved after treatment. DCI: Distal contractile integral; IRP: Integrated relaxation pressure.

not yet established. In our patient with a rare esophageal motility disorder and depression, antianxiety and antidepressant agents relieved his symptoms. However, the duration of treatment with antidepressants in patients with jackhammer esophagus and longer follow-up need further discussion.

ARTICLE HIGHLIGHTS

Case characteristics

A 60-year-old man with a 1-year history of intermittent and recurrent episodes of dysphagia, chest pain and heartburn, who had taken PPIs for a long time, but without relief of any symptoms.

Clinical diagnosis

Dysphagia, chest pain and heartburn and depressive state.

Differential diagnosis

Achalasia, gastroesophageal reflux disease, esophageal infections, esophageal carcinoma, coronary heart disease.

Laboratory diagnosis

All laboratory parameters were within normal limits.

Imaging diagnosis

High-resolution manometry (HRM) showed six swallows with distal contractile integral (DCI) > 8000 mmHg-s-cm in 10 liquid swallows and integrated relaxation pressure (IRP) 14.7 mmHg.

Pathological diagnosis

Esophageal mucosa appeared as ectopia of gastric mucosa.

Treatment

Deanxit for 6 mo, gradually reduced until withdrawal.

Related reports

Jackhammer esophagus is a rare disorder, and current treatments are limited, such as botulinum toxin injection, peroral endoscopic myotomy, and balloon dilatation.

Term explanation

Jackhammer esophagus is a rare esophagus disorder, and patients with extreme phenotypes of esophageal hypercontractility present mainly with dysphagia, chest pain, and gastroesophageal reflux symptoms. Jackhammer esophagus is described by a new Chicago Classification version 3.0 with at least two swallows with DCI > 8000 mmHg-s-cm.

Experiences and lessons

Patients with esophageal hypercontractility present mainly with dysphagia, chest pain, and HRM is the primary diagnostic method. Patients may also have mental illness, so at the time of diagnosis, psychological evaluation is necessary. Antianxiety and antidepressant agents are promising medical treatment to relieve symptoms in patients with jackhammer esophagus combined with psychosocial problems, but longer follow-up is needed.

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