ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2016 July 25; 8(14): 477-500

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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2014-2017

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WJGE World Journal of Gastrointestinal Endoscopy

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
July 25, 2016

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i14.477

World J Gastrointest Endosc 2016 July 25; 8(14): 477-488
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

2016 Gastrointestinal Endoscopy: Global view

Video capsule endoscopy in inflammatory bowel disease

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Author contributions: Collins PD analysed the literature and wrote the manuscript.

Conflict-of-interest statement: The author has no conflict of interest to report.

Manuscript source: Invited manuscript

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Received: March 27, 2016
Peer-review started: March 29, 2016
First decision: April 19, 2016
Revised: May 10, 2016
Accepted: June 1, 2016
Article in press: June 16, 2016
Published online: July 25, 2016

Abstract

Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel, which hitherto had been relatively inaccessible to direct visualisation. VCE has been shown to play a role in monitoring the activity of small bowel Crohn's disease and can be used to assess the response to anti-inflammatory treatment in Crohn's disease. For those patients with Crohn's disease who have undergone an intestinal resection, VCE has been assessed as a tool to detect post-operative recurrence. VCE may also aid in the reclassification of patients with a diagnosis of Inflammatory Bowel Disease Unclassified to Crohn's disease. The evolution of colon capsule endoscopy (CCE) has expanded the application of this technology further. The use of CCE to assess the activity of ulcerative colitis has been described. This advance in capsule technology has also fuelled interest in its potential role as a minimally invasive tool to assess the whole of GI tract opening the possibility of its use for the panenteric assessment of Crohn's disease. VCE is a safe procedure. However, the risk of a retained capsule is higher in patients with suspected or confirmed Crohn's disease compared with patients having VCE examination for other indications. A retained video capsule is rare after successful passage of a patency capsule which may be utilised to pre-screen patients undergoing VCE. This paper describes the use of VCE in the assessment of inflammatory bowel disease.

Key words: Video capsule endoscopy; Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Patency capsule

Core tip: Video capsule endoscopy (VCE) has evolved to become an important tool for the non-invasive examination of the small bowel. Prior to the development of this technology, the small bowel had been relatively inaccessible to direct visualisation. In the setting of Crohn's disease, VCE has been shown to play a role in monitoring disease activity and response to treatment. The evolution of colon capsule endoscopy has expanded the application of this technology in inflammatory bowel disease (IBD). This paper describes

the use of VCE in the assessment of IBD.

Collins PD. Video capsule endoscopy in inflammatory bowel disease. *World J Gastrointest Endosc* 2016; 8(14): 477-488 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i14/477.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i14.477

INTRODUCTION

Since its development over a decade ago, small bowel video capsule endoscopy (VCE) has evolved to become an important tool for studying the small bowel. VCE directly visualises the mucosal surface of the small bowel that is relatively inaccessible to gastroscopy and ileocolonoscopy, and does so in a minimally invasive manner. Its position in the investigation of gastrointestinal conditions varies according to the condition and is complementary to other investigations of the small bowel.

Among patients undergoing VCE, the assessment of known Crohn's disease or the investigation of suspected Crohn's disease, is often cited as the second most common indication for VCE[1]. The development of colon capsule endoscopy (CCE) has further expanded the potential applications of capsule technology to include the assessment of colonic inflammatory bowel disease (IBD).

In this article, the role of VCE in the diagnosis and assessment of IBD will be reviewed.

TECHNOLOGY

The first small bowel VCE system, M2A, later rebranded as PillCam SB, was developed by Given Imaging Limited (Yokneam, Israel) and was approved for use in 2001. Since then several other VCE systems, sharing a similar component set-up, have been developed (MiroCam, Intromedic, Seoul, South Korea; Endocapsule, Olympus Optical Co, Tokyo, Japan; OMOM capsule, Jinshan Science and Technology Group, Chongqing, China)[2]. In each system, the capsule is ingested and images are transmitted from the capsule to a sensing system attached to a data recorder, upon which real-time images may be viewed if required. Data are later transferred from the recorder to a computer for subsequent review of the images. A further system, CapsoCam, differs from the other VCE devices. It obtains 360° images and information is stored within the capsule itself[2]. The capsule is retrieved after it has been expelled and the information is downloaded wirelessly.

VCE FEATURES OF SMALL BOWEL CROHN'S DISEASE: MAKING THE DIAGNOSIS

The mucosal features of small bowel Crohn's disease that may be seen at capsule endoscopy include erythema, aphthous ulceration, loss of villi, villous oedema, mucosal fissures and strictures[3]. These findings are not specific to Crohn's disease, however, and may be seen in patients with other types of small bowel enteropathy.

There is, therefore, a potential risk for misinterpretation of inflammatory lesions seen at VCE. A non-selective approach to investigating patients may be associated with both a low yield from VCE examination and also may risk over-interpretation of small bowel findings[4,5]. Histological confirmation may be thought of as the gold standard when diagnosing Crohn's disease. However, this may be difficult to achieve in patients in whom the mucosal changes are located in an area that is difficult to access endoscopically. The clinical context in which inflammatory lesions are seen within the small bowel is therefore an important factor for clinicians interpreting VCE findings.

Non-steroidal anti-inflammatory drug (NSAID)-associated enteropathy is, for example, the commonest mimic of Crohn's disease of the small bowel and, for this reason, patients undergoing VCE assessment are advised to avoid taking NSAIDs for 4 wk prior to the procedure[2]. Despite this, surreptitious intake of NSAIDs has been reported in 13.6% of patients attending for VCE[6].

Other enteropathies that share similar mucosal appearances to Crohn's disease of the small bowel include small bowel lymphoma, radiation enteropathy, intestinal tuberculosis, Behcet's disease and enteropathy related to human immunodeficiency virus-associated opportunistic infections[7].

A further challenge to the interpretation of VCE findings is the recognition that lesions of the small bowel may be observed in healthy individuals. In a prospective randomised placebo-controlled study examining the incidence of NSAID-induced small bowel injury, 13.8% of healthy volunteers were found to have mucosal erosions at baseline[8]. In addition, it was also observed that 7% of healthy volunteers with a negative initial VCE within the placebo group developed mucosal breaks after a 2-wk period. It would appear therefore that not only do small bowel lesions occur in a significant proportion of healthy subjects, but they may also appear and regress over time.

The International Conference on Capsule Endoscopy (ICCE) have formulated an algorithm to aid in the diagnosis of Crohn's disease[9]. Patients are defined as having suspected Crohn's disease based on several clinical criteria. According to these criteria, a patient is considered to have suspected Crohn's disease if they have chronic diarrhoea, weight loss, abdominal pain or failure to thrive plus one other criterion in the form of extraintestinal symptoms raising a suspicion of Crohn's disease, evidence of elevated inflammatory biomarkers or abnormal imaging suggestive of Crohn's disease.

In a retrospective study of patients undergoing VCE for suspected Crohn's disease, those fulfilling ICCE criteria

Table 1 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Capsule Endoscopy Crohn's Disease Activity Index

A: Inflammation	B: Extent	C: Stricturing	Score for each segment
0 = None 1 = Mild to moderate oedema/hyperaemia/ denudation 2 = Severe oedema/ hyperaemia/denudation 3 = Small ulcer (5 mm) 4 = Moderate ulcer (5-20 mm) 5 = Large ulcer (20 mm)	0 = None 1 = Focal 2 = Patchy 3 = Diffuse	0 = None 1 = Single (passed) 2 = Multiple (passed) 3 = Obstructing	A × B + C

were more likely to be diagnosed with Crohn's disease during follow-up and had a higher burden of inflammation within the small bowel compared to those not fulfilling the ICCE criteria[5]. Twenty-one point four percent (6 of 28 patients) and 60.7% (17 of 28 patients) received a diagnosis of Crohn's disease during follow-up in the group of patients not meeting ICCE criteria and in the group meeting the criteria, respectively ($P < 0.05$).

VCE APPEARANCES IN SMALL BOWEL CROHN'S DISEASE

Scoring systems assessing the inflammatory burden in Crohn's disease

Scoring systems quantifying the burden of small bowel inflammation have been developed in an attempt to refine and standardise the way in which findings at VCE are reported. The two commonest scoring systems used in the literature are the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) and the Lewis score. Both scores quantify the severity and extent of small bowel inflammation.

CECDAI (Table 1)

Three elements of VCE findings contribute to the CECDAI scoring system. The small bowel is divided into two equal segments and a score generated for each segment based on the parameters of inflammation, extent and stricturing. The CECDAI is the sum of the scores for the two segments. Niv *et al*[10] have described the validation of this score in a prospective study.

Lewis score (Table 2)

The Lewis score is a semiquantitative validated scoring system used to assess the burden of small bowel inflammation and is the most commonly used scoring index[11]. The small bowel transit time is divided into three equal parts. Each tertile is scored separately according to the formula: Tertile score = (Villous appearance × Extent × Descriptor) + (Ulcer number × Extent × Descriptor). The score for the most severely affected tertile is added to the stenosis score (Stenosis number × appearance × Traversed score). The final score (Maximum Tertile Score + Stenosis Score) is the Lewis (Table 2)[11]. A score of < 135 correlates with clinically insignificant inflammation, a score of 135-790 correlates with mild inflammation and scores of ⩾ 790 correlate with moderate to severe inflammation.

The Lewis score is a measure of inflammatory activity and does not imply a diagnosis. However, the magnitude of the score may play a role in assessing the likelihood of Crohn's disease accounting for the lesions seen[5,12]. A score of ⩾ 135 was associated with a Crohn's diagnosis in 82.6% of patients undergoing VCE for suspected Crohn's disease. In contrast, only 12.1% of those with a Lewis score of ⩽ 135 received a diagnosis of Crohn's ($P < 0.05$)[5].

In a retrospective study assessing the diagnostic accuracy of the Lewis score in patients with suspected Crohn's disease, 58 patients met the ICCE criteria[12]. Within this group, a Lewis score of ⩾ 135 had a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of Crohn's disease of 89.5%, 78.9%, 73.9% and 91.8%, respectively.

VCE IN SUSPECTED CROHN'S DISEASE

The diagnosis of Crohn's disease is made on the basis of a clinical picture that encompasses biomarkers of inflammation, clinical symptoms and targeted investigations[13].

Colonoscopy with ileal intubation is advised as the first line investigation for the diagnosis of Crohn's disease as it will enable the diagnosis of Crohn's disease to be made in the majority of patients. However, 30% of patients will have Crohn's disease restricted to the small bowel that will be beyond the reach of the ileocolonoscope[14]. It is in this group of patients that VCE may useful in establishing a diagnosis of Crohn's disease[2].

The role of VCE in investigating patients in whom Crohn's disease is suspected is complementary to other modes of examination. Cross-sectional small bowel imaging has the advantage of providing information about transmural disease and extra-intestinal features that may include fistulae, collections and significant stricturing disease[3]. However, VCE is able to detect subtle mucosal lesions that may not be detected on small bowel radiological examinations.

In a meta-analysis assessing the yield of VCE *vs* other modalities for changes in keeping with Crohn's disease, VCE performed better than computed tomography enterography (CTE) and small bowel radiography[15]. The incremental yield of VCE examination in patients with suspected or established Crohn's disease compared to CTE and small bowel radiography was 39% ($P < 0.00001$, 95%CI: 27%-50%), and 37% ($P < 0.00001$, 95%CI: 29%-45%), respectively. For magnetic resonance (MR) enterography, VCE for examination of patients with suspected or established Crohn's disease was not demonstrated to be superior to VCE, with a non-significant incremental yield for VCE of 7% ($P = 0.23$,

Table 2 Scoring systems for the assessment of inflammatory burden in Crohn's disease: Lewis score

Parameter		Weightings (Calculated for each tertile)	
Villous appearance	Appearance	Longitudinal extent	Descriptors
	0 = Normal	8 = Short segment	1 = Single
	1 = Oedematous	12 = Long segment	14 = Patchy
		20 = Whole tertile	17 = Diffuse
Ulcer	Number	Longitudinal extent	Descriptors
	0 = None	5 = Short segment	9 = Less than 25% of circumference
	3 = Single	10 = Long segment	12 = 25% to 50% of circumference
	5 = Few	25 = Whole tertile	18 = Greater than 50% of circumference
	10 = Multiple		
Parameter		Weightings (Rated for the whole study)	
Stenosis	Number	Appearance	Passage of capsule past stricture
	0 = None	24 = Ulcerated	7 = Traversed
	14 = Single	2 = Non-ulcerated	10 = Not traversed
	20 = Multiple		

Short segment: ≤ 10% of the tertile; Long segment: 11%-50% of a tertile; Whole tertile: ≥ 50% of the tertile; Few: Two to seven lesions; Multiple: Eight or more ulcers, two or more stenoses.

95%CI: -4%-17%.) However, only four trials assessing VCE and MR enterography were available for inclusion in the meta-analysis and included only a small number of patients. This raises the possibility of a Type Ⅱ error. VCE performed better than the endoscopic modalities of ileocolonoscopy and push enteroscopy with an incremental yield of 22% (P = 0.009, 95%CI: 5%-39%) and 57% (P < 0.00001, 95%CI: 43%-71%). Some caution must be drawn in interpreting these results, however, as the absence of a reference or gold standard for diagnosis may have resulted in a confirmation bias favouring VCE with false positive examinations potentially contributing to the incremental diagnostic yield.

Jensen *et al*[16] addressed the issue of confirmation bias by comparing the diagnostic yield of VCE, MR enterography and CTE with ileocolonoscopy and/or surgery as the gold standard for assessing Crohn's. The authors reported a sensitivity and specificity for Crohn's disease affecting the terminal ileum of 100% and 91% for VCE, 81% and 86% for MR enterography and 76% and 85% by CTE, respectively. VCE was superior to both CT or MR small bowel studies for detecting lesions within the proximal small bowel (P < 0.05).

Leighton *et al*[17] compared the diagnostic yield of VCE *vs* small bowel barium follow-through (SBFT) and ileocolonoscopy in a prospective trial of 80 patients with suspected Crohn's disease. SBFT perfomed less well than the other two modalities. The combination of VCE with ileocolonoscopy detected more inflammatory lesions than the combination of SBFT and ileocolonoscopy [(97.3% and 57.3% of all inflammatory lesions identified, respectively (P < 0.01)]. Among the 25 patients with a final diagnosis of Crohn's disease, based on the physicians' global assessment of the findings of all three modalities, 11 were diagnosed with Crohn's disease on the basis of VCE findings alone, 5 by ileocolonoscopy findings alone but none by SBFT findings alone.

The place of VCE in a diagnostic algorithm for Crohn's disease is not completely clear. If used as a third line investigation after ileocolonoscopy and small bowel imaging, it is not cost-effective[18]. For those in whom Crohn's is suspected, VCE would miss stricturing or penetrating disease which has been reported in 25% of patients at diagnosis[19]. However, as the above studies illustrate, radiological small bowel assessment is inferior to VCE for detecting proximal inflammatory lesions within the small bowel.

VCE IN PATIENTS WITH KNOWN CROHN'S DISEASE

In patients with an established diagnosis of Crohn's disease, VCE has some advantages over other modalities for assessing inflammatory activity. VCE has the potential to identify the presence of active disease that may not be evident from conventional biomarkers, or to identify mucosal lesions that are not visible on radiological imaging. Of patients with Crohn's colitis, 25.6% of patients will also have disease affecting the small bowel[20]. VCE has a role in visualisation of the mucosa beyond the reach of the ileocolonoscope, and is superior to MR and CTE for the detection of small bowel disease[16,21]. This is of prognostic significance, as detection of proximal small bowel disease in patients with Crohn's disease has been associated with poorer clinical outcomes[22,23].

As indicated above, VCE does however, have some limitations compared to cross-sectional imaging of the small bowel for the assessment of small bowel involvement with known Crohn's disease in that only the mucosal surface is visualised. Further, visualisation of the small bowel may be incomplete in up to 25% of patients[24]. However, earlier versions of the video capsule had battery lives that were limited to only 6-8 h. Improvements in the battery life of the most recent iterations of the video capsule would be expected to enable an extended duration of the examination in patients

with the longest transit times. It would be expected that this would translate into a lower rate of incomplete examination.

Correlation of VCE findings with clinical symptoms and biomarkers of inflammation

Clinical symptoms can correlate poorly with the activity of IBD[25]. C-reactive protein (CRP) and faecal calprotectin are inflammatory biomarkers that are frequently used to assess and monitor the activity of IBD. It is recognised that CRP's usefulness as a surrogate marker in IBD can be limited in some patients, however. It is normal in up to 49% of patients with active ulcerative colitis (UC) and in up to 30% of those with Crohn's disease, CRP is not elevated during relapses of disease[26-28].

Several studies have investigated the degree to which findings at VCE correlate with inflammatory biomarkers. Niv *et al*[29] assessed the correlation between laboratory and clinical markers of disease activity and findings at VCE in patients with active Crohn's disease. Forty-three studies were performed in 19 patients. No correlation was demonstrated between the Lewis score and CRP. A similarly poor correlation between the Lewis score and clinical symptoms as assessed by the Crohn's Disease Activity Index (CDAI) and Inflammatory Bowel Disease Questionnaire (IBDQ), was reported.

Faecal calprotectin has a stronger correlation with mucosal inflammation than CRP with a reported sensitivity and specificity for the detection of mucosal disease of 70%-100% and 44%-100%, respectively[26]. Its reliability in the assessment of small bowel mucosal inflammation may be less good than for colonic disease[28,30], although some centres have reported an equivalent efficacy for assessing small bowel and colonic inflammation[31].

Koulaouzidis *et al*[32] described the outcome of 70 patients in whom isolated small bowel Crohn's disease was suspected. All patients had undergone a negative ileocolonoscopy and gastroscopy. No patients with a faecal calprotectin value below 100 had active inflammation in keeping with Crohn's disease[32]. In those with a calprotectin of > 200, the diagnostic yield was 65%. The same group reported a moderate correlation between faecal calprotectin and the Lewis score (r = 0.448, P = 0.0014)[33]. When the analysis was restricted to patients with a faecal calprotectin of < 100 a strong correlation was reported (r = 0.68, P = 0.0047). There was no significant correlation between CECDAI and calprotectin (r = 0.245, P = 0.089).

In a multicentre cross-sectional study assessing 187 patients undergoing VCE, significant small bowel inflammation (defined as Lewis score of > 790) correlated poorly with elevation of faecal calprotectin, CRP or a combination of both markers (r = 0.2; P = 0.14)[20]. On the basis of these data, the use of elevated biomarkers as a triage tool would have missed Crohn's in 40% of patients with moderate to severely inflamed small bowel.

Kopylov *et al*[34] assessed the inflammatory burden in the small bowel in patients with Crohn's disease in clinical remission, defined as those with a CDAI score of < 150. In line with previous observations that the absence of clinical symptoms does not reliably indicate a low inflammatory burden, 44 of 52 (84.6%) patients in clinical remission had significant mucosal inflammation of the small bowel (Lewis score > 135). Of the 21 patients in clinical remission who also had inflammatory biomarkers with a normal range (faecal calprotectin and CRP), 14 (67%) had significant mucosal inflammation of the small bowel (Lewis score > 135). The correlation between faecal calprotectin and the Lewis score was stronger than between CRP and mucosal inflammation (r = 0.39, P = 0.003 *vs* r = 0.28, P = 0.036, respectively). Both biomarkers had a high positive predictive value but low negative predictive value for the presence of moderate to severe inflammation (Lewis score $\geqslant$ 790) (96.2% and 24.1%, respectively, for faecal calprotectin; and 100% and 20.5%, respectively, for CRP).

The reported correlation between the Lewis score and biomarkers of inflammation is therefore variable, with the strongest correlation reported for calprotectin levels < 100[33]. In calculating the Lewis score, only the inflammatory score from the tertile with the most severe inflammation contributes to the final score. This may, in part, explain the variable correlation reported between faecal calprotectin and the Lewis score. That is, mild inflammation in the other two tertiles could reasonably be expected to contribute to an elevation in faecal calprotectin, but would not contribute to an elevation in the overall endoscopic score of inflammation[20]. For Crohn's patients in clinical remission, a stronger correlation between a cumulative Lewis score (using a summation of the individual tertile scores) and faecal calprotectin than the correlation between the conventional Lewis score and faecal calprotectin was demonstrated (r = 0.483, P = 0.001 and r = 0.39, P = 0.003, respectively)[34]. The use of a cumulative score requires further investigation.

Mucosal healing and VCE

Mucosal healing, as demonstrated at colonoscopy, has become established as an important endpoint for treatment in Crohn's disease. It has been associated with improvements in quality of life and in clinically relevant outcomes including rates of hospitalisation, rates of surgery and sustained steroid-free remission[35,36]. Although, there are fewer data on the prognostic significance of small bowel mucosal inflammation as assessed by VCE (see below), it is not unreasonable to infer that an improvement in VCE features of small bowel inflammation would also lead to better outcomes. Mucosal healing and the restoration of mucosal barrier function prevents the translocation of bacteria and the subsequent pathological inflammatory response[37]. It has been observed that in those with Crohn's

affecting both the colon and small bowel, improvement in the mucosal appearances in one section of the gastrointestinal tract may not parallel improvement in other locations[38].

Although a "gold standard" for small bowel mucosal healing in Crohn's disease has not yet been established[39], a Lewis score of < 135 is accepted as representing clinically insignificant inflammation[11]. This has been correlated with a CECDAI score of less than 3.8[33].

VCE findings as a predictor of disease outcome

Long *et al*[40] reported on the outcomes of 86 patients with Crohn's disease undergoing VCE. Severe findings, defined as multiple aphthous ulcers or stenosis, as compared to minimal or no inflammatory change, was associated with the addition of new medication (58.5% *vs* 22.2%, $P < 0.01$), and also with the likelihood of surgery (21.9% *vs* 4.4%, $P = 0.01$) in the 3 mo following the examination. Similarly, in study of 53 patients with Crohn's restricted to the small bowel, moderate-to-severe inflammation (defined as a Lewis score of ⩾ 790) was associated with an increased risk of corticosteroid therapy and hospitalisation during a mean follow-up period of 42 mo [RR = 5 ($P = 0.011$; 95%CI: 1.5-17.8) and 13.7 ($P = 0.028$; 95%CI: 1.3-141.9), respectively][41]. There was a trend towards surgery in patients with a Lewis score ⩾ 790 that was not statistically significant. It appears, therefore, that the severity of inflammation as quantified by the Lewis score may predict a more aggressive course of the disease in patients with Crohn's disease.

Disease location has also been identified as a predictor of disease outcome with proximal disease predicting clinical relapse in a retrospective review of 108 VCE examinations in patients with Crohn's disease[23].

Impact of VCE findings on clinical decisions

As the role of VCE in the assessment of Crohn's disease has expanded, several studies have described the impact of the findings at VCE on clinicians' clinical decisions.

In a retrospective study of small bowel capsule tests performed in 71 patients undergoing VCE for assessment of their Crohn's disease, the findings at VCE led to a change in medical therapy in 38 of 71 patients within 3 mo of the investigation[42]. Similarly, in a study that included 86 patients with Crohn's disease, an alteration in therapy occurred in 62% of patients as a consequence of findings from VCE within the 3 mo after the procedure. In 40%, this took the form of a new anti-inflammatory medication, the most common of which was a corticosteroid[40]. Cotter *et al*[43] reported in a retrospective study of 50 patients that, in the 3-mo period after VCE examination, 44% of patients initiated new IBD medication. the proportion of patients on a thiopurine or biologic increased in their cohort from 4% to 30%.

In the largest of the studies describing the impact of the findings at VCE on disease management data were collected on 187 patients undergoing VCE for assessment of known Crohn's disease[20]. Fifty-two point three percent of patients had their management altered as a consequence of the VCE findings. Initiation or dose-intensification of anti-inflammatory medications was undertaken in 82.5% of patients.

Impact of Crohn's treatment on small bowel inflammation as assessed by VCE

A small number of studies have described the impact of Crohn's treatments on small bowel appearances at VCE[44-46].

In a prospective study of 40 patients treated for a flare of Crohn's disease, VCE was performed at baseline and after at least four weeks of treatment, the choice of which was at the discretion of the treating physician[46]. All patients showed a clinical response. However, of the endoscopic variables assessed, only the number of large ulcers showed a statistically significant improvement after treatment [8.3 ± 1.4 and 5 ± 0.8 (mean ± SEM), before and after treatment, respectively (mean difference 3.3 ± 1.2, 95%CI: 0.8-5.9, $P = 0.01$)]. No patients achieved mucosal healing within the 4-wk period of treatment period examined.

In another small prospective study, 43 patients with active Crohn's were offered VCE assessment, following which they were offered additional treatment. In contrast to the short follow-up period in the previous study, 37 patients underwent a further VCE examination at week 12, and 28 patients underwent VCE at week 52[44,45]. Eighty-four percent received Adalimumab and 16% azathioprine. At initial assessment, 33% had mild disease (CECDAI score < 3.5) and the remainder moderate to severe disease (CECDAI score ⩾ 5.8). At 12 wk, 54% were in clinical remission. None had achieved complete mucosal healing, but the CECDAI had normalised in 27% of patients. Significant reductions in median faecal calprotectin and CRP values were observed. At 12 mo, 42% had complete mucosal healing.

Assessment of post-operative recurrence

Asymptomatic recurrence of Crohn's disease after resection is a common occurrence. Seventy-three percent of patients undergoing ileal resection have endoscopic recurrence in the neoterminal ileum one year after surgery[47]. Eighty percent of patients of these patients were symptom free. Some IBD experts advocate routine endoscopic assessment 6 mo post-operatively and offer a step-up in treatment to those with significant recurrence (Rutgeerts score ⩾ i2)[48].

Conflicting results have been reported in two prospective studies comparing the superiority of VCE or ileocolonoscopy for the detection of recurrent disease in patients who have previously had an ileocolonic resection. However, both studies reported that VCE detected lesions in the small bowel beyond the reach of

the ileocolonoscope in up to two thirds of patients[49,50].

ROLE OF VCE IN THE RECLASSIFICATION OF IBD

The term, Inflammatory Bowel Disease Unclassified (IBDU) is conventionally used to classify patients with an intact colon in whom colonic biopsies are not able to distinguish between UC and Crohn's disease. Following a diagnosis of IBDU approximately 30% of patients will be reclassified as Crohn's disease during follow-up[51]. It is not possible to distinguish between UC and Crohn's disease on histological examination of the resection specimen in up to 15% of patients with colitis undergoing colectomy[52]. These patients are conventionally classified as having indeterminate colitis.

These observations have implications for the monitoring and treatment of IBD in these patients. VCE aid in the reclassification of the diagnosis to Crohn's disease which is of particular relevance, for example, to patients in whom the formation of an ileoanal pouch is being considered as rates of pouch failure are higher in patients with Crohn's disease compared to UC or indeterminate colitis[53].

Mow *et al*[54] described the use of VCE in patients with an established diagnosis of IBD who had previously undergone radiological assessment of the small bowel. Twelve of 21 patients with UC or IBDU were reclassified has having probable Crohn's disease after VCE. In this study, Crohn's disease was defined as the presence of small bowel ulcers that were serpiginous, deep-fissuring, coalescing, linear or nodular. Patients with multiple small or indistinct ulcers could also be classified as having Crohn's disease. Similarly, Mehdizadeh *et al*[55] 2008 reported that 19 of 120 patients with IBDU or UC were found to have VCE findings consistent with Crohn's disease (defined as three or more ulcers in the small bowel). In both these studies, the reclassification of patients as having Crohn's disease was based on the identification of inflammatory lesions within the small bowel. However, it should be noted that a negative VCE examination does not exclude a reclassification of IBDU to Crohn's disease. In a cohort of 30 patients with IBDU, a subsequent diagnosis of Crohn's disease (5 patients) and UC (one patient) was made at ileocolonoscopy after a negative VCE examination[56].

In a paediatric population, higher rates of reclassification of IBDU and UC to Crohn's disease have been reported, with more than 50% having their diagnosis revised after VCE[57,58].

CCE

The technology

In an extension of the technology that had been developed to examine the small bowel, a wireless capsule endoscopy system has been developed examination the colonic mucosa. CCE uses a capsule that differs slightly from the small bowel capsule. The wider diameter of colon means that the tendency of the capsule to flip around its axis is greater. A second camera was added in order that both ends of the capsule could capture images simultaneously. Advances in battery technology have extended the battery life sufficiently for the capsule to capture images of the entire colon. The most recent version of the CCE, the PillCam COLON 2 (Given Imaging, Yokneam, Israel) has an angle of view of 172°[59].

Standard bowel cleansing regimes used for conventional colonoscopy are insufficient for examination of the colon with CCE. The bowel cleansing regime for CCE includes 4 L polyethylene glycol. During the procedure, further boosters based on sodium phosphate are used in order to enhance the propulsion of the capsule through the small bowel and colon[60].

CCE in Crohn's disease

CCE has been assessed as a tool for assessing colonic inflammation in active Crohn's disease. In a study prospectively following 40 patients with Crohn's disease, all patients underwent colonoscopy and CCE[61]. There was substantial agreement between the Crohn's Disease Endoscopic Index of Severity (CDEIS) scores calculated using both modalities [intraclass correlation coefficient (ICC), 0.65; 95%CI: 0.43-0.80]. There was also a substantial inter-observer agreement for CDEIS scores (ICC, 0.67; 95%CI: 0.35-0.86). Agreement between the two modalities of examination was less good for Simplified Endoscopic Score for Crohn's Disease (SES-CD). However, CCE appeared to systematically underestimate of the severity of disease. The greatest agreement between colonoscopy and CCE was observed in the ileum (ICC, 0.73; 95%CI: 0.54-0.85) with a trend towards poorer agreement towards the distal colon. The sensitivity for the detection of ulcers within the colon was 86%. However, a low specificity for colonic ulceration of 40% indicates that CCE may not be an adequate tool to assess mucosal healing. In common with other studies of CCE, patients found CCE examination to be more tolerable than optical colonoscopy.

Although, CCE was developed as a tool to assess the colonic mucosa, images of the entire GI tract are captured. This has prompted interest in investigating a potential role for CCE's effectiveness in assessing both the large and small bowel[62]. It's potential role as a single minimally invasive tool to assess the entire gastrointestinal (GI) tract in Crohn's is appealing. A small study assessing the efficacy of CCE for panenteric evaluation of Crohn's disease reported the outcomes for 12 patients with Crohn's disease in steroid-free remission[63]. The entire GI tract could be visualised in 10 of the 12 patients. The use of CCE identified isolated SB disease in three patients.

CCE in UC

Several studies have addressed a potential role for CCE

as a minimally invasive investigation for the assessment of the activity of UC. In the largest of the studies, 100 patients with suspected or confirmed UC were assessed with CCE and colonoscopy[64]. CCE was had a sensitivity and specificity for the detection of colonic inflammation of 89% and 75%, respectively. In a prospective study including 26 patients with UC, CCE compared to colonoscopy showed a moderate agreement for assessing extent of disease and a substantial agreement for the assessment of severity of disease (κ = 0.522, P < 0.001 and κ = 0.751, P < 0.001, respectively)[65]. Hosoe *et al*[66] reported a strong correlation between CCE and colonoscopic assessment of the severity of inflammation (average ρ = 0.797).

There are several limitations in the use of CCE to assess UC. UC may only involve the distal colon and an incomplete CCE examination would fail to identify inflammatory pathology in these patients. In common with VCE of the small bowel, the inability to obtain biopsy specimens is a further limitation. Its role in UC would therefore not encompass surveillance for dysplastic change or scenarios in which biopsies to exclude superadded CMV infection are required.

COMPLICATIONS OF VCE

Capsule retention

Capsule retention, defined as the failure of the video capsule to pass through the GI tract after 2 wk, is a significant concern for clinicians who perform capsule endoscopy. It is more common in patients undergoing VCE for suspected or definite Crohn's disease. In a systematic review which included 2538 VCE procedures performed in patients with definite or suspected Crohn's disease, a capsule retention rate of 2.6% was reported in this group, compared to an overall retention rate of 1.4% in 22840 VCE procedures as a whole[24].

In patients with a retained capsule due to a Crohn's inflammatory stricture, a short course of steroids may enable the capsule to pass spontaneously. However, most patients with a retained capsule may require endoscopy or surgery to retrieve the capsule[67]. Surgical retrieval has been reported to be necessary in 53%-100% of cases of capsule retention. In one small study of 12 patients with a retained capsule, of whom 8 had a Crohn's-associated stricture, double balloon enteroscopy avoided the need for surgery in 75% of cases[68].

Strategies to reduce the risk of capsule retention in IBD

Among patients with Crohn's disease undergoing VCE assessment, those thought to be at highest risk of capsule retention include those with extensive small bowel disease, small bowel strictures, previous abdominal surgery and those with a prior history of small bowel obstruction. Conventional small bowel imaging (small bowel barium studies, CTE and MR enterography) or assessment with a patency capsule (PC) (see later) are useful adjuncts to identify small bowel features that may contraindicate the use of VCE.

However, in one study examining the use of PC assessment of the small bowel (see below), the authors assessed the use of selective PC assessment[69]. Those at higher risk of capsule retention were defined as those patients with obstructive symptoms, previous small bowel resection or bowel obstruction, or those deemed to require a PC by the referring clinician. Interestingly, a selective selection strategy *vs* a non-selective strategy did not correlate with the risk of retention of the video capsule.

Small bowel imaging and prediction of capsule retention

Among patients with an established diagnosis of Crohn's disease, CTE or MR enterography may identify stenotic lesions that would contraindicate VCE in 27%-40% of patients[70]. However, capsule retention may still occur if small bowel imaging misses clinically significant stricturing disease. In a retrospective study of 50 patients with a confirmed diagnosis of Crohn's disease, for example, 6% of the patients had capsule retention despite normal cross-sectional small bowel imaging studies and no history of obstructive symptoms[43].

PC

The Agile PC (Given Imaging Limited, Yokneam, Israel) was developed for use as a pre-screening tool to reduce the risk of capsule retention in patients undergoing VCE. The PC is the same size and shape as the video capsule. It consists of a core containing lactose and 10% barium, the latter component rendering the capsule radio-opaque. The core is contained within a cellophane wrapping with hollow wax plugs at each end of the capsule. Enteric fluid pass through the hollow wax plugs and the capsule disintegrates after 30 h[71]. The PC contains a radiofrequency emitter that can be detected by a hand-held scanner. If, after 30 h, the PC is detected, then its position within the GI tract can be assessed radiologically.

Video capsule retention is a rare occurrence after a negative PC test with retention rates of between 0.6% and 2.1% reported after a satisfactory PC assessment[20,69,72].

There are a number of possible explanations for the observation that the video capsule may become retained after a negative PC test. Rapid disintegration of a PC leading to false negative patency test and subsequent VCE retention has been reported[73]. Assadsangabi *et al*[72] utilized low-dose CT scanning to assess the position of the PC. In the single case of video capsule retention that occurred in this study, the PC was seen to have been retained in a dilated, faecalised segment of ileum that had been misinterpreted as a segment of colon[72].

A positive PC test is associated with a significant risk of video capsule retention. The retention rate in 18 patients with established Crohn's disease who underwent a VCE examination after a positive PC test was 11.1% (P = 0.01)[69].

Adverse effects of PC include abdominal discomfort which has been reported to occur in 20% of patients with established Crohn's disease in one series[69]. Surgical intervention for small bowel obstruction secondary to retention of a PC has been reported[71,74,75]. It is thought that this may arise if the PC lodges in such a way that the enteric luminal contents are unable to access the lactose core of the PC.

A retrospective study of 42 patients undergoing PC and radiological assessment demonstrated a similar sensitivity and specificity for both tests for detecting significant small bowel stricturing [sensitivity for patency and radiological tests of 57% and 71%, respectively (P = 1.00) and specificity of 86% and 97%, respectively (P = 0.22)][76].

Current European guidelines advise use of a PC prior to VCE in patients with a confirmed diagnosis disease[2].

Other complications of VCE

The handful of cases of perforation reported in patients undergoing investigation with VCE have largely occurred in patients with capsule retention and an established diagnosis of Crohn's disease[77]. Aspiration of the video capsule occurs rarely, and has been reported in 1 in 800 examinations[78].

CONCLUSION

VCE has evolved into an important complementary tool to investigate the small bowel in patients with suspected or established Crohn's disease. It is a minimally invasive and well tolerated test with a high diagnostic yield. Its place in the monitoring of Crohn's disease and the implications of VCE findings for the treatment of Crohn's disease are becoming better understood. The more recent development of CCE has expanded the potential applications of capsule endoscopy to include assessment of UC and to provide a pan-enteric assessment of patients with Crohn's disease.

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P- Reviewer: Otowa Y, Toth E **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

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DOI: 10.4253/wjge.v8.i14.489

World J Gastrointest Endosc 2016 July 25; 8(14): 489-495
ISSN 1948-5190 (online)

Endoscopic full thickness resection for gastric tumors originating from muscularis propria

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Author contributions: Jain D contributed to literature review, interpretation of data and drafting of the manuscript; Mahmood E contributed in acquisition of data, interpretation of data and drafting of the manuscript; Desai A contributed in acquisition of data; Singhal S contributed to literature review and critical revision of the manuscript for important intellectual content.

Conflict-of-interest statement: None of the authors have any conflicts of interest.

Data sharing statement: Our article is a systematic review and thus it does not apply to our article.

Manuscript source: Invited manuscript

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Received: March 6, 2016
Peer-review started: March 7, 2016
First decision: April 6, 2016
Revised: May 6, 2016
Accepted: May 31, 2016

Article in press: June 2, 2016
Published online: July 25, 2016

Abstract

AIM: To do systematic review of current literature for endoscopic full thickness resection (EFTR) technique for gastric tumors originating from muscularis propria.

METHODS: An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered. For the purpose of review, data from individual studies was combined to calculate mean. No other statistical test was applied.

RESULTS: A total of 9 original articles were identified. Four articles were from same institute and the time frames of these studies were overlapping. To avoid duplication of data, only the study with patients over the longest time interval was included and other three were excluded. In total six studies were included in the final review. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%. The mean procedure time varied from a minimum of 37 min to a maximum of 105 min. There was no reported mortality from the technique itself. The most common histological diagnosis was gastrointestinal stromal tumors and leiomyoma. Gastric wall defect closure by either metallic clips or over the scope clip (OTSC) had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm).

CONCLUSION: EFTR is a minimally invasive technique to resect gastric submucosal tumors originating from muscularis propria with a high success rate and low complication rate.

Key words: Endoscopic full thickness resection; Gastric tumor; Muscularis propria; Over the scope clip

Core tip: Endoscopic submucosal dissection success for gastric submucosal tumors arising from muscularis propria has remained limited. Authors have reported success with endoscopic full thickness resection (EFTR) in achieving complete resection of gastric tumors (as large as 5 cm) originating from musucularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of patients. Careful selection of candidates by preoperative imaging and endoscopy including endoscopic ultrasound to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

Jain D, Mahmood E, Desai A, Singhal S. Endoscopic full thickness resection for gastric tumors originating from muscularis propria. *World J Gastrointest Endosc* 2016; 8(14): 489-495 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i14/489.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i14.489

INTRODUCTION

Over the last decade, therapeutic options for gastric submucosal tumor (SMT) resection have drastically evolved. Gastric SMTs are mostly asymptomatic when small (< 2 cm) and are discovered incidentally on endoscopy or radiological investigations done for other indications but larger lesions are more likely to be symptomatic[1]. The usual symptoms are bleeding, abdominal pain or obstruction. Abdominal mass and weight loss may be present especially if malignant[2].

Gastrointestinal SMTs can be broadly classified in 4 main groups - gastrointestinal stromal tumors (GIST) which should be considered potentially malignant; smooth muscle derived SMTs like leiomyoma, leiomyosarcoma; SMTs of neurogenic origin like schwannoma, granular cell tumor, neurofibroma and vascular tumors like hemangioma, lymphangioma, kaposi sarcoma, *etc*[3]. GISTs are further classified into groups based on their potential of recurrence and metastasis; very low risk, low risk, intermediate risk and high risk or overtly malignant with metastasis at diagnosis[4]. Most of the tumors arising from muscularis propria are GISTs[5]. National Comprehensive Cancer Network Guidelines recommend resection of GISTs larger than 2 cm[6]. Gastric SMTs smaller than 2 cm without clinical signs of malignancy can be managed conservatively with frequent follow up by endoscopic ultrasonography (EUS)[7]. However, conservative management is limited by patient's anxiety about diagnosis and follow-up compliance. In addition, EUS cannot differentiate between benign and malignant tumor reliably and EUS-guided fine-needle aspiration is not always accurate since histology is not available[8]. Due to these reasons some physicians and patients may prefer resection of these tumors over conservative management.

Surgically, gastric SMTs can be resected either by laparoscopic approach or open procedure. However, less invasive endoscopic techniques have been considered and used more often in the last few years. The endoscopic techniques include snare polypectomy or endoscopic submucosal dissection (ESD). Not all SMTs arising from muscular propria may be luminal to be suitable for snare polypectomy and the success rate for complete resection of tumors originating from muscularis propria by ESD has been reported to vary from 68% to 75%[9,10]. As tumors from muscularis propria are deep and are associated with risk of perforation and incomplete resection with ESD, newer techniques like full thickness resection followed by endoscopic closure of defect have evolved.

In this review article, we have summarized the studies describing endoscopic full thickness resection (EFTR) of gastric SMTs originating from muscularis propria. Indications, procedure techniques, outcomes and complications reported are discussed.

MATERIALS AND METHODS

An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered.

RESULTS

A total of 9 original articles were identified. Four articles[11-14] were from same institute and the time frames of these studies were overlapping. Only, the study[11] which included the patients over the longest time interval was included in our review. Other three were excluded to avoid duplication of data[12-14]. Out of the final 6 studies included, one was a prospective study[15] from Germany and other 5 were retrospective studies[11,16-19] from China. One study[15] reported results for all gastric sub epithelial tumors. However, we included only those patients from this study who had tumors originating from muscularis propria[15]. All studies have been summarized in Table 1.

Table 1 Descriptive summary of all studies

Ref. and location	Study type	Inclusion criterion	Exclusion criterion	No. of subjects	No. of lesions	Tumor location	Mean size of lesion (range) (cm)	Mean procedure time (range) (min)	Complications	Success rate (%)	Follow up
Ye *et al*[11], 2014 China	Retrospective Single Centre	(1) CT/EUS confirmation of MP origin (2) No extraluminal growth	(1) Size > 3.5 cm (2) Coagulation disorders (3) Unfit for GA (4) High risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity)	51	51	(1) Fundus = 22 (2) Corpus = 28 (3) Antrum = 1	2.4 (1.3-3.5)	52 (30-125)	None	98	(1) Surveillance endoscopy for healing at 1, 3 and 6 mo PP (2) For GIST = Endoscopy/ EUS/ abdominal ultrasound/ CT/chest radiography every 12 mo, indefinitely
Schlag *et al*[15], 2013 Germany	Retrospective Single Centre	(1) Age > 18 yr (2) Confirmed SET originating from MP on EUS	(1) Size > 3.0 cm (2) ASA class 4 or 5 (3) Coagulopathy (4) Pregnancy	EFTR group = 6	6	(1) Corpus = 4 (2) Antrum = 1 (3) Cardia = 1	1.3 (0.7-2.0)	37.3 (26-45)	None	83.3	(1) Telephone interview or outpatient visit at 1 mo PP (2) Endoscopy at 3 mo PP
				Lap group = 5	5	(1) Fundus = 1 (2) Corpus = 4	1.88 (0.8-2.6)	55 (30-95)	None	80	
Feng *et al*[16], 2014 China	Retrospective Single Centre	(1) MP originating tumor confirmed on EUS or CT if size > 2.0 cm	(1) Size > 5.0 cm (2) Coagulopathy (3) Patients not suitable for GA	48	52	(1) Fundus = 40 (2) Corpus = 7 (3) Antrum = 1	1.59 (0.50-4.80)	59.72 (30-270)	(1) Abdominal distension = 5	100	(1) Endoscopy at 2, 6, 12 and 24 mo PP
Guo *et al*[17], 2015 China	Retrospective Single Centre	(1) CT and EUS confirming origin of tumor from MP	(1) Size > 2.0 cm (2) Enlarged lymph nodes (3) Malignant disease	23	23	(1) Fundus = 11 (2) Corpus = 9 (3) Antrum = 3	1.21 (0.6-2.0)	(1) Mean ETFR time = 40.5 (16-104) (2) Mean closure time = 4.9 (2-12)	(1) Loocalised peritonitis = 2 (managed conservatively) (2) Post op fever = 4	100	(1) Endoscopy at 1 wk, 1 and 6 mo PP
Wu *et al*[18], 2015 China	Retrospective analysis of clincal control study	(1) Single tumor (2) Absence of metastasis	(1) Size > 5.5 cm	EFTR group = 50	50	(1) Fundus = 14 (2) Corpus = 23 (3) Antrum = 13	3.4 (2.5-5.0)	85 (55-155)	None	100	(1) Endoscopy at 1 mo PP
				Lap group = 42	42	(1) Fundus = 8 (2) Corpus = 19 (3) Antrum = 15	3.8 (3.0-5.0)	88 (45-215)	(1) Gastroparesis = 2 (managed conservatively)	93	
Zhou *et al*[19], 2011 China	Retrospective Single Centre	(1) MP originating tumors confirmed on EUS	(1) Size > 5.0 cm (2) Patients not fit for GA (3) Known abdominal adhesions	26	26	(1) Fundus = 12 (2) Corpus = 14	2.8 (1.2-4.5)	105 (60-145)	None	100	(1) Endoscopy at 2, 4 and 6 mo PP and then every 6 mo (2) EUS or CT scan was performed if tumor residual or recurrence was suspected

GA: General anesthesia; MP: Muscularis propria; PP: Post procedure; SET: Subepithelial tumor; EFTR: Endoscopic full thickness resection; Lap: Laparoscopic; CT: Computed tomography; EUS: Endoscopic ultrasonography; GIST: Gastrointestinal stromal tumors; ASA: American society of anesthesiologists.

DISCUSSION

Indications

All studies included patients with gastric SMTs originating from the muscularis propria confirmed on pre procedure imaging. Endoscopic EUS was the standard imaging technique used in all the studies to determine the layer of origin and size of tumor. Most studies[11,17-19] also included computed tomography (CT) imaging to further assess the tumor and look for any metastasis. In one study, CT scan was performed only if the tumor size was > 2.0 cm on EUS[16]. Small size gastric tumors arising from MP can be either benign or malignant. EUS does not allow definite discrimination of benign from malignant lesions[20,21]. Even tissue sampling by EUS guided fine needle aspiration, trucut biopsy or other biopsy techniques fails to reliably differentiate between benign and malignant lesions[22-29]. Hence, the only accurate way is complete resection of the target lesion. Nonetheless, authors from each study have used any potential sign of malignancy like large regional lymph nodes, metastatic disease on CT scan, large tumor size, high risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci or heterogeneity) as an exclusion criteria. In addition, subjects with coagulopathy and those unfit for endotracheal intubation or general anesthesia were also excluded.

The inclusion and exclusion criteria for subjects across each study have been summarized in Table 1.

Technique

Ye *et al*[11], Feng *et al*[16], Guo *et al*[17], Wu *et al*[18] and Zhou *et al*[19], used similar technique with little variations to resect the gastric SMTs from muscularis propria. Both single and dual channel endoscopes were used to resect the tumor. Dual chamber endoscope was especially used for the broad based tumors. A transparent cap was applied to the tip of the endoscope to provide a constant endoscopic view during the procedure. The area around the lesion was marked either by needle knife[11,19] or argon plasma coagulation[18]. Submucosa in the area around the lesion was injected with a solution containing normal saline, 1% indigo carmine and epinephrine to make dissection easier. A hook knife[11,16,18], IT knife[16] or a triangle tipped knife[17] was used to make incision in mucosa over the tumor. Dissection down to the serosa was done using hook knife and IT knife. Gastric fluid was aspirated and an active perforation was made through with a hook knife or IT knife. The tumor was dissected out *en bloc*. A needle paracentesis was often performed for decompression if there were signs of pneumoperitoneum.

Schlag *et al*[15] performed EFTR *via* slightly different technique. EFTR was performed under the laparoscopic control in general anesthesia unless contraindicated, in which scenario procedural sedation was used. A 5 mm optic was used for laparoscopic control. A double channel endoscope was used in all cases. The tumor was grasped by the tissue anchor and lifted into the snare. The snare was secured and resection performed using blended electrosurgical current. Some of the cases developed perforation during resection, which was treated with tissue twin grasper and over the scope clip (OTSC).

Sarker *et al*[30] attempted EFTR for gastric tumors (n = 2, both were less than 2 cm in size) using OTSC. Although the study was excluded from the review secondary to the site of tumor origin (above the level of muscularis propria), the technique used by the author deserves a mention. The target gastric lesion was suctioned into the cap, followed by deployment of OTSC. Following clip application the scope was removed and reintroduced to snare the lesion above the closed clip. In both cases, author was able to achieve tumor free margin but was unable to achieve full thickness resection. With further improvisation, OTSC holds a promising future for achieving EFTR for local gastric tumors. For larger defects post resection two OTSC placed side by side can be helpful[31].

Closure

It is extremely important and challenging to achieve effective closure of the gastric perforation for the success of procedure to prevent peritonitis and surgical intervention. There were two main methods for gastric defect closure-metal clips[11,16,18,19] and OTSC[15,17].

Metal clips have been commonly used to close the gastric wall defect. They can be easily applied when the perforation is small. For wider defects, air suctioning was used to narrow the size of defect and then clips were applied to close the defect[11,18,19]. In few cases across the studies, omental patch method[18,19] was used in which the omentum was sucked into the gastric cavity and clips were used to seal the wound by clipping the omentum to the gastric mucosa. This technique is useful especially for larger defects. Ye *et al*[11] used endoloop to further strengthen the closure with clips. The endoloop was placed to trap all clips, the loop was tightened and all the clips were tied together with a ligature[11]. The number of clips used for gastric wall closure were higher for the tumors located in the gastric corpus[16].

OTSC closure system has been used in the past for the treatment of gastrointestinal bleeding, fistulas and perforations. Guo *et al*[17] and Schlag *et al*[15] used OTSC system to close the perforation after tumor resection. Gastric tissues adjacent to the perforation were clamped and then drawn into the transparent cap of the OTSC device. The OTSC system was then released to close the defect. Metal clips were used for any remaining perforation. Both closure methods-clips and OTSC have been found to be effective in the studies. OTSC system is simple to use, convenient and quick however the maximum tumor size for which it has been used till now is 3 cm in the study by Schlag *et al*[15]. The use of OTSC for gastric perforations arising from EFTR of larger gastric SMTs originating from muscularis propria has not yet been reported.

The protocols to check for leak varied in different studies. Contrast roentgenography was routinely conducted on day 3 by Ye *et al*[11]. In the study where, EFTR was performed under laparoscopic control, methylene blue was used at the end of the procedure to perform leakage test[15]. Feng *et al*[16] and Guo *et al*[17] did not report any routine post op investigations to check for the adequacy of closure. Two other studies reported use of contrast roentgenography on day 3 to check for contrast leakage in addition to abdominal and pelvic ultrasound to check for any fluid collections[18,19].

As there is no uniform protocol, it needs to be established what type of investigations need to be performed routinely if any.

Procedure time

The mean procedure time varied from a minimum of 37 min[15] to a maximum of 105 min[19]. It was noted that EFTR for SMT > 2.0 cm and for gastric corpus located SMTs took longer time[16]. Schlag *et al*[15] who used grasp and snare technique had shorter procedure time as compared to the other studies who used dissection for full thickness resection. Wu *et al*[18] had a mean time of 85 min for EFTR as compared to 88 min for laparoscopic surgery for gastric SMT originating from muscularis propria. A number of factors including size of tumor, location, technique used and experience of operator may effect the procedure time.

Post op care

The immediate post op care in most studies included GI decompression with nasogastric tube, NPO for 1 to 3 d, Proton Pump Inhibitors and antibiotics. Zhou *et al*[19] used hemocoagulase injections in addition to the above mentioned post op management.

Outcome

The success of procedure was considered as the complete resection of the tumor and closure of the perforation endoscopically without the need to convert into surgical operation during or after the procedure. R0 is complete resection of tumor with clear margins microscopically while R1 is macroscopic complete resection but positive margins on histology. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%.

Ye *et al*[11] reported a success rate of 98% for the 51 patients included in the study. One patient in this study needed laparoscopy to retrieve the tumor as it fell in the peritoneal cavity[11]. Feng *et al*[16] reported a tumor free margin resection rate of 100%. A total of 52 lesions in 48 patients were resected in this study with a mean tumor size of 1.59 cm (0.50-4.80 cm)[16]. Guo *et al*[17] also reported a success rate of 100% for tumor free margins for all 23 lesions. The mean size of the tumor was 1.21 cm (0.6-2.0 cm)[17]. Wu *et al*[18] included 50 patients in their study who had EFTR of SMTs with a mean size of 3.4 cm (2.0-5.0 cm) and 42 patients who had laparoscopic procedure for gastric SMTs with a mean size of 3.8 cm (3.0-5.0 cm). They reported a success rate of 100% for EFTR as compared to 93% for laparoscopic resection. In 3/42 patients, the laparoscopic procedure needed to be converted to laparotomy due to the location of the tumors[18]. Zhou *et al*[19] also achieved a success rate of 100% for their 26 patients with a mean tumor size of 2.8 cm (1.2-4.5 cm). Schlag *et al*[15] who performed grasp and snare technique had 20 patients in their study. Eleven out of 20 patients had muscularis propria originating tumors with mean size of 1.56 cm (0.7-2.6 cm). In 5/11 patients, a pure endoscopic approach appeared impossible and a switch to laparoscopic gastric wedge resection was made. The main reasons were extraluminal growth and large size. So endoscopic resection was performed in 6/11 patients. Of these 6 patients, R0 resection was achieved in 5/6 patients (83.3%) and R1 in 1/6. R0 resection rate in laparoscopic group was 80% (4/5 patients). One patient had acute myeloid leukemia (AML) and histology showed diffuses infiltration of AML recurrence in gastric wall. Routine CT scanning in the pre procedure workup was not included in the protocol of this study. The high conversion rate to laparoscopy due to location and size of tumor may suggest the need of extensive pre procedure imaging to better define the size and location of the tumor to plan the resection modality.

Complications

Most studies[11,15,18,19] did not report any major complications and the post procedure recovery was unremarkable. Feng *et al*[16] reported abdominal distension in 5 patients. It was relieved with paracentesis in 3 patients and resolved in 2 d in the rest of the patients. Guo *et al*[17] reported post op fever in 4 patients and localised peritonitis in 2 patients, which was managed conservatively. Overall, the complication rate was low with no mortality and no major complications.

Histopathology

The most common diagnosis was GIST and leiomyoma. Out of 51 total lesions, Ye *et al*[11] found 30 lesions to be GIST (7 - very low risk and 23 - low risk) and 21 to be leiomyoma. Schlag *et al*[15] removed 11 tumors arising from muscularis propria. The histolopathologic examination showed GIST in 4, ectopic pancreas in 2, lipoma in 1, accessary spleen in 1, leiomyoma in 1, angioma in 1 and acute myeloid infiltration in 1 specimen. Feng *et al*[16] reported a diagnosis of GIST in 43 patients (29 - benign; 8 - very low risk and 6 - low risk), leiomyoma in 4 and schwannoma in 1. In the study by Guo *et al*[17] the histology of 23 cases revealed GISTs in 19 (18 - very low risk and 1 - high risk) and Leiomyoma in 4 cases. Zhou *et al*[19] resected 26 lesions. Of these 16 were GIST (2 - benign; 12 - low risk; 2 - malignant), 6 were leiomyoma, 3 were glomus tumor and 1 was schwanoma.

GISTs can be malignant but imaging techniques including EUS and CT scan cannot reliably estimate the malignant potential. Thus, resection of these gastric SMTs with minimal invasive techniques is necessary to make a histological diagnosis and estimate risk of malignancy without increasing the morbidity.

Follow up

All authors performed upper GI endoscopy on follow up visits, however timing varied across the studies[11,15-19]. None of the authors reported any recurrence on the follow up visits. Currently, there is no uniform agreed follow up protocol after EFTR of gastric SMTs arising from muscularis propria. Although endoscopy alone is used in all studies for follow up, there may be a role of EUS to detect recurrence in deeper layers, which may be missed on routine endoscopy.

ESD success for gastric SMTs arising from muscularis propria has remained limited. Incomplete resection and high incidence of perforation seen with ESD is likely secondary to deep location of the tumor. Authors have reported success with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of gastric SMTs. Careful selection of candidates by preoperative imaging and endoscopy including EUS to rule out metastatic disease and to confirm the size and location of lesion remains crucial. Gastric wall defect closure by either metallic clips or OTSC had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm). Post resection follow up by EUS in addition to endoscopy is contemplated. The overall evidence for EFTR for gastric SMTs originating from muscularis propria is small but promising and more experience is awaited.

COMMENTS

Background

Minimally invasive resection of local gastric lesions has remained a challenge for endoscopists. Over the last decade, newer techniques like endoscopic mucosal resection (EMR), piecemeal EMR (EPMR), endoscopic submucosal dissection (ESD) have come up.

Research frontiers

For subset of gastric tumors originating from muscularis propria, the success of ESD remains limited due to deeper location resulting in incomplete resection and increased incidence of perforation. Endoscopic full thickness resection (EFTR) seems to have overcome these pitfalls.

Innovations and breakthroughs

Authors have reported high success rate with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications.

Applications

EFTR seems to be a reasonable replacement for laparoscopic technique for resection of gastric submucosal tumors. Careful selection of candidates by preoperative imaging and endoscopy including endoscopic ultrasonography to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

Terminology

EFTR is a minimally invasive method for *en bloc* resection of gastrointestinal lesions.

Peer-review

This is a good summarization of classification and option of therapeutic method of submucosal tumors (SMTs). The necessity of EFTR for SMTs is convincing and the outcome of EFTR is satisfactory and promising.

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P- Reviewer: Bleve C, Ilhan E, Lee HW, Zhang QS
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v8.i14.496

World J Gastrointest Endosc 2016 July 25; 8(14): 496-500
ISSN 1948-5190 (online)

CASE REPORT

Splenic artery aneurysm presenting as a submucosal gastric lesion: A case report

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Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Saint Joseph University.

Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

Manuscript source: Invited manuscript

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Received: March 18, 2016
Peer-review started: March 21, 2016
First decision: May 17, 2016
Revised: May 23, 2016
Accepted: June 14, 2016
Article in press: June 16, 2016
Published online: July 25, 2016

Abstract

We are reporting the rare case of splenic artery aneurysm of 4 cm of diameter presenting as a sub mucosal lesion on gastro-duodenal endoscopy. This aneurysm was treated by endovascular coil embolization and stent graft implantation. The procedure was uneventful. On day 1, the patient presented an acute severe epigastric pain and cardiovascular arrest. Abdominal computed tomography scan showed an active leak of the intravenous contrast dye in the peritoneum from the splenic aneurysm. We performed an emergent resection of the aneurysm, and peritoneal lavage. Postoperatively, hemorrhagic choc was refractory to large volumes replacement, and intravenous vaso-active drugs. On day 2, he presented massive hematochezia. We performed a total colectomy with splenectomy and cholecystectomy for ischemic colitis, with spleen and gallbladder infarction. Despite vaso-active drugs and aggressive treatment with Factor VIIa, the patient died after uncontrolled disseminated intravascular coagulation.

Key words: Gastroscopy; Splenic artery aneurysm; Rupture; Endo-vascular treatment; Surgery

Core tip: Recently, a per-cutaneous endovascular embolization procedure has become the first-line treatment for splenic artery aneurysm. This rare presentation, in this case, as sub-mucosal gastric lesion and bleeding after embolization of the aneurysm showed the gravity of this entity when the diameter of aneurysm is > 2 cm. Although the risk of rupture is low, ruptured splenic artery aneurysm carry a high mortality rate.

Tannoury J, Honein K, Abboud B. Splenic artery aneurysm presenting as a submucosal gastric lesion: A case report. *World J Gastrointest Endosc* 2016; 8(14): 496-500 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i14/496.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i14.496

INTRODUCTION

Splenic artery aneurysms (SAA) are a rare clinical entity that carry the risk of rupture and fatal hemorrhage (particularly those sized > 2 cm). SAA accounts for up to 60% of all splanchnic artery aneurysms and is the third most common intra-abdominal aneurysm following those of the aorta and the iliac arteries[1-7]. The diagnosis is often incidental on abdominal radiologic exams[7-12]. Symptomatic SAA (20%) may present with abdominal pain in the epigastrium or left upper quadrant. A more dramatic mode of presentation is spontaneous rupture of the aneurysm which is reported to occur in 2%-10% of patients as the initial presentation[1-12]. We report here a case of an 82-year-old man with SAA presenting as a sub mucosal lesion on upper gastro-duodenal endoscopy. We will discuss diagnosis tools of SAA, management and potential complications.

CASE REPORT

An 82-year-old male patient with a history of hypertension and smoking presented with vague epigastric pain. General physical examination was unremarkable. All labs were within normal limits. He underwent a diagnostic upper gastro-intestinal endoscopy and it showed a 5-cm firm non pulsating submucosal lesion in the fundus suggesting gastrointestinal stromal tumor (GIST) (Figure 1). Endoscopic ultrasound was then performed to characterize the sub mucosal lesion and to perform biopsies. It showed a round anechoic cystic mass measuring 3.5 cm in diameter, communicating with the splenic vessels and showing positive flow on Doppler ultrasound, suggesting a splenic artery aneurysm. Abdominal enhanced computed tomography (CT) scan and angioscan revealed a dilated and tortuous course of the splenic artery with a first saccular aneurysm of 20 mm of diameter behind the stomach lesser curvature, and a second saccular aneurysm of 43 mm of diameter projecting into the stomach (Figure 2). *Via* a femoral artery catheterization, the patient underwent an endovascular coil embolization and stent graft implantation to treat the aneurysms. The angiographic series taken after the procedure was satisfactory. The procedure was uneventful, and the patient was hemodynamically stable for the first few hours after endovascular repair. On day 1 post embolization, the patient presented an acute severe epigastric pain with rapid drop in arterial pressure and cardiovascular arrest. He was successfully resuscitated and intubated. An urgent abdominal enhancing CT scan revealed active extravasation of the intravenous contrast dye in the peritoneum from the splenic aneurysm confirming the diagnosis of ongoing peritoneal bleeding (Figure 3). We performed an emergent laparotomy with resection of the aneurysm, and peritoneal lavage. The patient is transferred to the intensive care unit. His hemorrhagic choc was refractory to large volumes of isotonic saline, multiple transfusions of packed red blood cells, fresh frozen plasma, platelets, and intravenous vaso-active drugs. On day 2, he presented massive hematochezia. A second laparotomy revealed an extensive ischemic colitis, with spleen and gallbladder infarction, as well as some hypo-perfused regions of the small intestine. We performed a total colectomy with splenectomy and cholecystectomy. Despite vaso-active drugs and aggressive treatment with Factor VIIa, the patient died after uncontrolled disseminated intravascular coagulation.

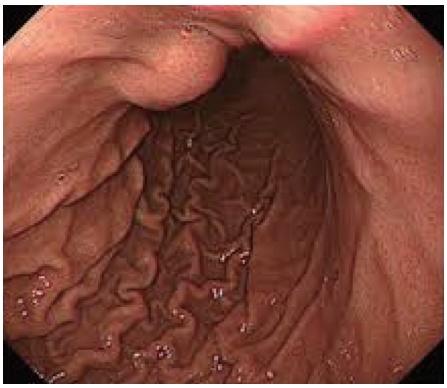

Figure 1 Gastrodudenal endoscopy showing a 5-cm firm non pulsating sub mucosal lesion in the fundus.

DISCUSSION

SAA diagnosis is nearly always a fortuitous discovery by abdominal imaging (CT scan and ultrasound). In our case, the initial presentation was a sub-mucosal non pulsatile lesion detected on an upper gastro-duodenal endoscopy. At our knowledge, this type of presentation has not been described in the literature. Endoscopic ultrasound was initially done with the purpose of performing a fine needle aspiration of the lesion, thought to be a gastric sub-mucosal tumor as GIST. However, the positive Doppler flow detected shifted the diagnosis to a vascular lesion instead of a sub-mucosal tumor, and therefore fine needle aspiration was not performed. The prevalence of SAA is reported to be 0.1%-2%; however, the number of undetected SAAs may be much higher. The clinical presentation is nonspecific in most cases, and the diagnosis of SAA is often an incidental finding[5]. SAAs account for up to 75% of all visceral artery aneurysms and are more commonly reported in female patients than in male patients at a ratio of 4:1. Why SAAs predominate in women is not exactly clear, but a hormonal contribution has been postulated[13]. The pathophysiology of SAA is not fully understood,

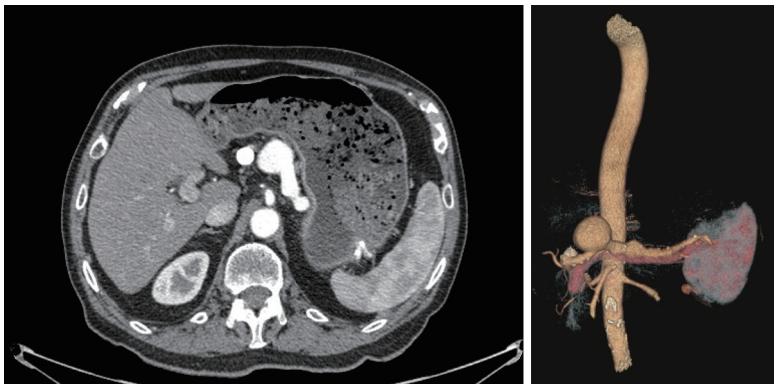

Figure 2 Abdominal enhanced computed tomography scan and angioscan showing a double aneurysm of splenic artery.

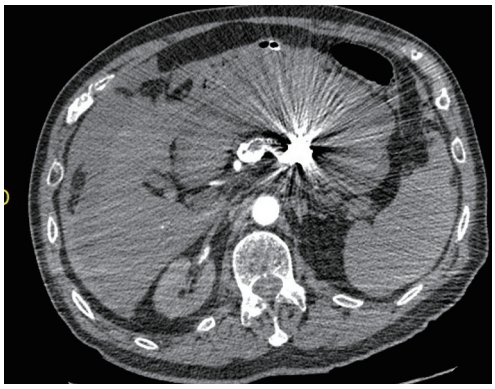

Figure 3 Abdominal enhanced computed tomography scan showing a peritoneal leak of contrast material from splenic aneurysm.

but local failure of the connective tissue of the arterial wall to maintain the integrity of the blood vessel could be playing a major role. Multiple risk factors have been listed including atherosclerosis, autoimmune diseases, collagen vascular diseases, pancreatitis, portal hypertension, traumatisms, fibromuscular dysplasia, female gender, and history of multiple pregnancies[11-16]. Nearly 70% of the SAA are saccular and situated at splenic hilum bifurcation[6]. Although the risk of rupture is low (nearly 2% of cases), ruptured SAA carry a high mortality rate, approaching 50%. Risk factors for rupture of the aneurysms include pregnancy, development of symptoms, expanding aneurysms, a diameter greater than 2 cm, portal hypertension, porto-caval shunt and liver transplantation[1,3,5,7,12]. Therefore, patients having one or more risk factor should undergo active treatment. Once the diagnosis of SAA is made, the essential goal of the physician remains to choose the adequate patient to treat as well as the right timing of any intervention. It is the general consensus that symptomatic SAA should be treated immediately, since rupture is associated with a high mortality rate. According to the guidelines, treatment is suggested for SAA with diameters > 2 cm or if the SAA is three times greater in diameter than the respective normal artery[5]. To treat symptoms and prevent complications, SAA repair is often required[4]. Various therapeutic options are available for patients with SAA, including conventional open surgery, endovascular treatment and, most recently, laparoscopic surgery[17-26]. Endovascular techniques (EV), including trans-catheter embolization and covered stent placement, can be used to treat most SAA regardless of the clinical presentation, etiology, or location of the aneurysm. If endovascular treatment is technically unavoidable, surgery should be considered given both good results and low morbidity. Open surgical treatment has traditionally been performed. The surgical procedures included ligation of the splenic artery, resection of the aneurysm and vascular reconstruction and/or bypass, and resection of the aneurysm with splenectomy. Complications rate of surgical treatment of non-ruptured aneurysm was 14.3%, and reached 25% in case with rupture[5]. The 30-d mortality rate of surgical treatment was 2.6% in non-ruptured aneurysm and 20.4% in rupture cases[13]. Recently, a per-cutaneous endovascular embolization procedure has become the first-line treatment for SAA. Packing of the aneurysmal sac with embolic agents (most commonly with coils, but also with detachable balloons and inert particles) and exclusion of the aneurysmal neck are the recommended techniques for treating splenic artery aneurysms. In our case, the patient had a 4 cm aneurysm and he was therefore treated with coil embolization and stent graft placement. Although trans-catheter arterial embolization (TAE) is associated with significantly lower morbidity and mortality than are surgical procedures, the possibility of organ ischemia or hemorrhagic events should not be underestimated. The success rate of TAE varies between 75% and 100%, with complication rate (aneurysm re-permeabilization, hemorrhage) ranging from 14% to 25%. The most common complications include acute pancreatitis, splenic infarction, splenic abscess, or intra-peritoneal hemorrhage. In case of an intra-peritoneal hemorrhage with hemodynamic instability, emergent laparotomy with resection of the aneurysm is the treatment of choice, with, however, high morbidity and mortality rate[5]. EV is the most cost-effective treatment for most patient groups with SAAs, independent of the sex and risk profile of the patient. EV is superior over OPEN in costs and effect for all age groups[4]. The results of meta-analysis show that EV of SAA has better short-term results than OPEN. However, OPEN is associated with fewer late complications and re-interventions during

follow-up. The results of this meta-analysis show that SAAs > 2 cm should be treated, given the good short-term and long-term results. EV repair has the best outcomes and should be the treatment of choice if the splenic artery has a suitable anatomy for EV repair[13]. In our case, the patient had peritoneal hemorrhage at day 1 post embolization requiring emergent laparotomy. Despite aggressive treatment, the patient died after uncontrolled disseminated intravascular coagulation. In a large cohort evaluating prognostic factors associated with the clinical outcomes after TAE, multivariate analysis confirmed advanced patient age, post procedure thrombocytopenia, post procedure hydrothorax, and the need for a second intervention to be significant prognostic factors for overall 30-d morbidity[13]. In our case, the patient's advanced age and the need for a second intervention after TAE were two prognostic factors associated with high short term morbidity and mortality.

In conclusion, SAA may be incidentally discovered on an upper gastro-duodenal endoscopy as a sub-mucosal lesion of the stomach. Caution must be made in order not to perform biopsies or fine needle aspiration to such lesions before checking for Doppler flow on endoscopic ultrasound. Treatment of choice for SAA of more than 2 cm of diameter is trans-catheter arterial embolization with a complication rate of around 20%. Intra-peritoneal hemorrhage after EV for SAA carry a high mortality rate despite emergent laparotomy and aggressive medical treatment.

COMMENTS

Case characteristics

An 82-year-old male patient with a history of hypertension and smoking presented with vague epigastric pain.

Clinical diagnosis

General physical examination was unremarkable.

Differential diagnosis

Gastrointestinal stromal tumor, pancreatic mass, gastric tumor.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Upper endoscopy showed a 5-cm firm non pulsating submucosal lesion in the fundus, and computed tomography showed two splenic artery aneurysms (SAAs).

Treatment

Endovascular coil embolization and stent graft implantation, and surgical excision.

Related reports

SAAs are a rare clinical entity that carry the risk of rupture and fatal hemorrhage (particularly those sized > 2 cm). The diagnosis is often incidental on abdominal radiologic exams. Symptomatic SAA (20%) may present with abdominal pain in the epigastrium or left upper quadrant. A more dramatic mode of presentation is spontaneous rupture of the aneurysm which is reported to occur in 2%-10% of patients as the initial presentation.

Experiences and lessons

SAA may be incidentally discovered on an upper gastro-duodenal endoscopy as a sub-mucosal lesion of the stomach. Caution must be made in order not to perform biopsies or fine needle aspiration to such lesions before checking for Doppler flow on endoscopic ultrasound.

Peer-review

The case is well presented though the language needs to be refined a little. It would be prudent if the authors elaborate a bit on the treatment options including operative mortality (elective *vs* emergent) and success rates of radiological interventions.

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P- Reviewer: Arora A, Vennarecci G **S- Editor**: Gong ZM
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