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REVIEW

Endoscopic palliation of malignant biliary obstruction

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Abstract

Malignant biliary obstruction often presents with challenges requiring the endoscopist to assess the location of the lesion, the staging of the disease, the eventual resectability and patient preferences in term of biliary decompression. This review will focus on the different modalities available in order to offer the most appropriate palliation, such as conventional endoscopic retrograde cholangiopancreatography, endoscopic ultrasound guided biliary drainage as well as ablative therapies including photodynamic therapy or radiofrequency ablation.

Key Words: Biliary obstruction; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasonography; Stenting; Ablation therapy

Core Tip: Endoscopic palliation of malignant biliary obstruction can often be challenging. Endoscopic retrograde cholangiopancreatography remains the gold standard for biliary decompression. Its widespread use and high success rate, especially in expert hands, makes it an effective modality for biliary decompression. Yet, recent advances in endoscopic ultrasound guided biliary drainage have emerged from a rescue therapy to a reliable tool with high technical and clinical success rates with moderate adverse event rates. Growing evidence suggest that this can be considered as a first line option in the future. Lastly, photodynamic therapy and radiofrequency ablation of the bile duct can also optimize stent patency, palliate symptoms and prolong survival. While there are limited head to head studies, radiofrequency ablation may be a more cost effective option with lower adverse events.

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INTRODUCTION

Palliation of unresectable malignant biliary obstruction is recommended to achieve biliary decompression and allow for symptomatic relief (*i.e.*, jaundice and pruritis). Minimally invasive endoscopic biliary drainage techniques have garnered significant attention as an effective patient friendly treatment option that can improve one's quality of life when comparing it to the more invasive nature of surgery and/or percutaneous transhepatic biliary drainage (PTBD) approaches. At the present, endoscopic retrograde cholangiopancreatography (ERCP) serves as the cornerstone of biliary decompression. However, in instances of failed or inaccessible cannulation endoscopic ultrasound guided biliary drainage techniques have emerged as second line options with comparable clinical outcomes. Furthermore, localized endobiliary ablative tools *via* photodynamic therapy and radiofrequency ablation have proven to be supplementary methods to palliate symptoms and optimize stent patency. As such this state-of-the-art review will shed light on palliative endoscopic modalities for the effective management of biliary drainage.

CONVENTIONAL ERCP

Malignant biliary obstruction can be categorized as a distal or hilar obstruction. This distinction is important as management options and outcomes differ. As such, the following two sections are subdivided to describe the ERCP approach in draining malignant distal biliary obstruction (MDBO) and malignant hilar biliary obstruction.

MDBO

MDBO represents a wide clinicopathologic spectrum of intrinsic and extrinsic bile duct compression arising within the pancreaticobiliary system. The most common etiologies are pancreatic adenocarcinoma and cholangiocarcinoma; in fact, up to 70% of patients with pancreatic cancer present with distal biliary obstruction[1,2]. Since the majority of patients are diagnosed at advance stages, management *via* palliative endoscopic decompression is increasingly encountered.

ERCP with transpapillary stenting is the gold standard for decompressing unresectable MDBO with a success rate of 90%-95%[3,4]. Palliative endoscopic biliary drainage is indicated as a means to treat cholangitis while providing symptomatic relief with improved quality of life measures[5,6]. As an established therapeutic modality for over 40 years, ERCP has emerged as a more effective and less invasive option compared to surgery and PTBD. While surgical bypass may decrease rates of recurrent jaundice, it is associated with a significant morbidity and mortality[2,7,8]. A meta-analysis of five randomized controlled trials (RCT) (379 patients) found that post-operative complications and 30 d mortality (16.3% *vs* 9.6%) were higher in surgical cohort[8]. In general many of these patients are poor operative candidates, whereby complications associated with surgical intervention can delay palliative chemotherapy options as well. Similarly, ERCP is often preferred over PTBD due to lower rates of adverse events, fewer re-interventions, decreased costs, shorter duration of hospital stay, and the lack of an external drain needed[4,6,9]. A large national database comparing 7445 ERCPs *vs* 1690 PTBD procedures at community and tertiary care centers associated lower adverse events with ERCP (8.6% *vs* 12.3%, $P < 0.001$) regardless of the centers PTBD volume of expertise[9]. There is also a risk of seeding metastasis with PTBD[10]. That being said, PTBD is typically used as rescue therapy in cases of ERCP failure (which we highlight later on the EUS-BD section).

Stent selection

In order to ensure long term stent patency, placing a self-expandable metal stents (SEMS) is a well-established and cost-effective approach for patients with a life expectancy greater than 3 mo[4,11,12]. The type of stents available include covered self-expandable metal stents (CSEMS) and uncovered self-expandable metal stents (USEMS). The optimal stent type remains uncertain due to varying RCTs with mixed results (Table 1)[13-21]. A recent meta-analysis of 11 randomized controlled trials involving 1272 patients (643 CSEMS and 629 USEMS) reported no significant difference in rates of recurrent biliary obstruction or mortality[22]. While there was a 32% risk reduction for stent failure and mortality favoring CSEMS, this possibly benefit was offset but higher rates of sludge formation and stent migration[22]. Another meta-analysis of 9 RCTs (1061 patients) found no difference in length of stent patency[23]. In terms of adverse events (including pancreatitis and cholecystitis), there appears to be no

Table 1 Covered versus uncovered self-expandable metal stents in malignant distal biliary obstruction

Ref.	Study design; country	Total number subjects	Number of SEMS Placed, CSEMS *vs* USEMS	Recurrent biliary obstruction; CSEMS *vs*USEMS, *n* (%)	Stent patency CSEMS *vs* USEMS, d	Procedure related adverse events, CSEMS *vs*USEMS, % (*n* = #)
Sakai *et al* [13], 2021	Multicenter randomized control trial; Japan	92	44 *vs* 48	10 (22.7%) *vs* 21 (43.8%), *P* = 0.0467	455 *vs* 301, *P* = 0.0112	6.8% (2 cholangitis, 1 cholecystitis) *vs* 8.3% (2 pancreatitis, 2 cholangitis), *P* = 0.549
Conio *et al* [14], 2018	Multicenter randomized control trial; Italy	158	78 *vs* 80	12 (16.7%) *vs* 10 (13.2%), *P* = 0.65	240 *vs* 541, *P* = 0.031	18% (6 cholangitis, 2 cholecystitis, 5 migrations) *vs* 7.9% (6 cholangitis), *P* = 0.061
Yang *et al* [15], 2015	Single center randomized control trial; South Korea	103	51 *vs* 52	17 (33.3%) *vs* 15 (28.8%), *P* = 0.623	395 *vs* 365, *P* = 0.467	17.6% (5 cholecystitis, 3 pancreatitis, 1 cholangitis) *vs* 9.6% (3 cholecystitis, 2 cholangitis), *P* = 0.378
Lee *et al* [16], 2013	Single center randomized control trial; South Korea	40	20 *vs* 20	10 (50%) *vs* 4 (20%), *P* = 0.047	207 *vs* 413, *P* = 0.041	5% (1 cholecystitis) *vs* 0%, NS
Lee *et al* [17], 2014	Retrospective, single center; USA	749	171 *vs* 578	33 (19%) *vs* 123 (21%), *P* < 0.001	468 *vs* 799, *P* = 0.61	8.2% (10 pancreatitis, 4 cholangitis) *vs* 6.4% (6 pancreatitis, 3 cholecystitis, 28 cholangitis), *P* = 0.20
Kitano *et al* [18], 2013	Multicenter randomized control trial; Japan	120	60 *vs* 60	14 (23%) *vs* 22 (36%), *P* = 0.08	583 *vs* 314, *P* = 0.019	3.3% (1 pancreatitis, 1 cholecystitis) *vs* 3.3% (2 cholecystitis), NS
Telford *et al*[19], 2010	Multicenter randomized control trial; Canada	129	68 *vs* 61	20 (29%) *vs* 11 (18%), NS	357 *vs* 711, *P* = 0.530	4.4% (3 cholecystitis) *vs* 6.6% (3 cholecystitis, 1 pancreatitis), *P* = 0.046
Kullman *et al*[20], 2010	Multicenter randomized control trial; Sweden	379	188 *vs* 191	47 (25%) *vs* 45 (24%), *P* > 0.50	154 *vs* 199, *P* = 0.326	7.5% (2 cholecystitis,3 pancreatitis, 8 cholangitis, 1 perforation) *vs* 10.5% (2 cholecystitis,4 pancreatitis, 12 cholangitis, 1 perforation, 1 hemorrhage), *P* = 0.370
Isayama *et al*[21], 2004	Single center randomized control trial; Japan	112	57 *vs* 55	8 (14%) *vs* 21 (38.2%), *P* < 0.001	304 *vs* 161, *P* < 0.05	12.3% (5 pancreatitis, 2 cholecystitis) *vs* 5.5% (1 pancreatitis, 2 hemorrhage), NS

NS: Not significant; USA: United States.

major differences based on stent type[23,24].

To combat tumor ingrowth and prolong stent patency, paclitaxel-incorporated drug eluting metal stents have been developed in South Korea. The stent is coated with membrane layers of polytetrafluoroethylene to prevent bile acid degradation and sodium caprate to enhance paclitaxel delivery[25]. A meta-analysis of 5 studies comparing drug eluting stents (197 patients) to SEMS (151 patients) reported a pooled stent patency of 168 d and 149 d, respectively[26]. There were no major differences in rates of cholangitis (17% *vs* 15%) or cholecystitis (6.5% *vs* 5.0%). Further studies are needed to determine if these drugs eluting stents can alter the management of MDBO. None of those stents have received FDA clearance so far.

Malignant hilar lesions

Malignant hilar obstruction poses its own set of unique challenges, especially since the endoscopic intervention is often technically challenging. In a large study analyzing 59437 ERCPs, successful outcomes and reduced adverse events were associated with high volume endoscopists and centers[27]. This highlights the importance of managing these patients in a high volume multidisciplinary center, as technical failure can significantly shorten the median length of survival compared to successful biliary drainage (8.7 mo *vs* 1.8 mo, *P* < 0.001) in type III and IV hilar cholangiocarcinoma[28].

Malignant hilar strictures can be categorized based on their extent of hilar and/or hepatic duct involvement *via* the Bismuth-Corlette classification system[29]. Since the majority of these strictures are inoperable with varying degrees of anatomical complexity, this classification can help guide the palliative approach for biliary decompression[30]. In general Bismuth grades I/II are amenable to ERCP, however grades III/IV are typically managed by a combination of ERCP and/or PTBD[4]. Choosing between ERCP and PTBD for types III/IV was analyzed in a meta-analysis of 9 studies (*n* = 546 patients) where there was a higher success rate seen with PTBD over ERCP in types III/IV with comparable rates of adverse events and 30 d mortality, unfortunately the skillset of the endoscopists involved in that study was not provided[31]. Another study of 110 patients with inoperable Bismuth type III/IV, found

that failure of endoscopic stenting was associated with an acute angulation at the common bile duct and intrahepatic duct[32]. While pre-operative imaging may help guide an approach, PTBD can be technically challenging in the setting of liver metastases, ascites, and if intrahepatic bile duct is not fully dilated; thus, ERCP remains the preferred modality for drainage[33].

Choosing between the two modalities is based on multiple factors ranging from local expertise, risk of infection, possible seeding by PTBD, life expectancy, comorbidities and patient preference regarding an external catheter[31]. While there have been studies with mixed results favoring ERCP[34] and PTBD [35,36] the optimal stenting technique should be guided by achieving ≥ 50% of total liver volume drainage in order to relieve jaundice and reduce the risk of cholangitis[37]. Previously it was thought that draining 25% of liver volume was sufficient; however another study found that at least 50% drainage was a predictor of effective drainage and longer overall survival (199 d *vs* 59 d), especially in Bismuth type III strictures[38]. Another retrospective study of 78 patients with unresectable type II-IV hilar strictures found that effective liver volume drainage correlated with liver function: in which biliary drainage ≥ 33% can be obtained with preserved liver function and ≥ 50% with impaired liver function [39]. In addition to liver function, the anatomical difference in liver volume may also effect drainage, as the right lobe accounts for 55%-60% of volume, followed by 30%-35% in left and 10% of the caudate lobes[40,41]. Consequently, utilizing bilateral or multi-sectoral stenting is typically advised in high grade strictures based on varying anatomical involvement of disease[4].

Unilateral vs bilateral drainage

Choosing unilateral and/or bilateral stenting is typically based on the patient's presentation, degree of obstruction and local anatomy. Pre-endoscopic imaging is also imperative to understand and calculate the liver volume drainage needed. It is well established that one stent provides sufficient drainage in Bismuth I. However, for Bismuth II-IV there is no clear consensus.

A recent metanalysis of 21 studies with 1292 patients comparing both techniques noted similar rates of clinical efficacy and complications for both unilateral and bilateral drainage though there were higher rate of technical success in the unilateral group (97% *vs* 89%, $P = 0.003$)[42]. However, these results were not analyzed based on the bismuth classification or etiology of obstruction. A multitude of studies have compared unilateral *vs* bilateral drainage with similar rates of success[43-47]. One multicenter RCT of 133 patients with Bismuth grades II-IV reported no major differences in technical success, however the bilateral group had longer duration of stent patency (252 d *vs* 139 d) and fewer rates of reinterventions (42.5% *vs* 60.3%, $P = 0.049$)[43]. Similarly, a retrospective study of 141 patients found that bilateral drainage portended a longer survival advantage (255 d *vs* 80 d, $P < 0.0001$)[45]. Such advantages come at the expense of higher rates of complications and risk of death with bilateral drainage, irrespective of Bismuth grade[44].

Bilateral stenting techniques

In order to ensure adequate drainage, bilateral stenting techniques using a stent-by-stent (SBS) or stent-in-stent (SIS) have been utilized, though there is no clear consensus on what technique is superior due to limited data. Following deployment of the intrahepatic bile duct a second stent can be placed parallel using the SBS method or sequentially through the mesh within in the initial stent using the SIS approach [37]. These are technically challenging procedures that require high levels of experience with technical success rates ranging from 73% to 100%[33]. One retrospective comparing SIS ($n = 40$) to SBS ($n = 24$) reported similar rates of technical success (100% *vs* 96%), clinical success (93% *vs* 96%) and rates of recurrent biliary (48% *vs* 43%)[48]. Though there was a higher rate of post-procedural related pancreatitis exclusively seen in the SBS group[48]. At the same time another study found no significant difference in early (31.6% *vs* 22.7%) or late (36.8% *vs* 50.0%) complications for SBS *vs* SIS[49]. This was also demonstrated in a meta-analysis of 158 patients that found no significant difference in technical success, complications or stent occlusion[50]. Many centers prefer the SBS approach since deploying multiple stents is relatively easier and in cases of stent dysfunction reintervention is possible[33,51]. Reintervention with plastic stents placed inside SEMS is also possible after the SIS approach. Recently a newly designed Y-shaped bilateral endoscopic stent has been investigated, though further studies are needed to better define its role in clinical practice[52-54]. At our center we use the SBS approach preferentially.

ENDOSCOPIC ULTRASOUND GUIDED BILIARY DRAINAGE

Since its introduction in 2001, EUS-guided biliary drainage (EUS-BD) has emerged as an effective and reliable alternative for managing malignant biliary obstruction[55]. While ERCP remains the current gold standard, it is associated with a failure rate of up to 10%-especially in cases of surgically altered anatomy (SAA), tumor infiltration/obstruction, periampullary diverticulum, prior duodenal stenting or stenosis[4,56,57]. However, unsuccessful ERCPs may vary based on institutional experience. Two studies with extensive ERCP expertise reported unsuccessful canulation in 0.60% to 0.68% of patients [58,59]. Of note, one of those studies described 3 out of 524 failed ERCPS in native papillas with limited

instances of SAA (n = 2) or duodenal obstruction (n = 3)[59]. On the other hand a large prospective study of 4561 patients from 66 hospitals (with varying degrees of expertise) found that 17.2% of ERCPs were unsuccessful[60]. The European guidelines recommend repeating ERCP in select patients, ideally two to four days after the first ERCP, with success rates up to 82%[4].

In instances of ERCP failure where salvage therapy is needed, PTBD has conventionally been pursued; however, as mentioned above it is associated with a significant morbidity, decreased quality of life and need for re-interventions. In this context EUS-BD emerged as another less invasive option with fewer procedure related adverse events (8.80% *vs* 31.22%, P = 0.022) and re-intervention rates (0.34 *vs* 0.93, P = 0.02) when compared with PTBD in a randomized open label study[61]. A meta-analysis with 483 patients confirmed these findings and found that while there was no difference in technical success, the EUS-BD group was associated with better clinical success, less reinterventions and fewer postprocedure adverse events[62].

EUS-BD is an appealing approach, though at the moment it is a specialized technique limited to a high-volume centers. In this regard understanding the associated learning curve is needed before its widespread applicability. A few studies have looked into this, and there appears to be a clear association with significantly decreased adverse events with increased operator procedural volume over time[10,63-67]. In a single center study with 215 procedures performed by one experienced endoscopist over a 6.6 year period, there was a notable decrease in adverse events as procedural volume increased each year[67]. Other studies have proposed that 33 and 100 cases were required to achieve technical proficiency and mastery, respectively[65,66].

The routes of biliary decompression can be accomplished through a rendezvous (RV), antegrade or transluminal (intra- or extrahepatic) approach[3]. The application of EUS-RV is limited to intact gastroduodenal anatomy, when conventional ERCP cannulation fails, in which a guidewire is accessed across the anastomosis in an antegrade fashion-this salvage approach is limited by a success rates of 74%-80% with a relatively high major adverse event rate of 11%[3]. Antegrade stenting has also fallen out of favor as it can be cumbersome with a limited technical success rate of 77%[3]. The puncture site (transgastric into left intrahepatic duct) allows for guidewire placement across the stricture/papilla without the need for fistula tract formation at the puncture site[68]. In instances of technical failure, antegrade stenting can be converted to transmural or PTBD[68]. Overall, direct transmural drainage is preferred *via* extrahepatic or intrahepatic approach.

Extrahepatic approach

EUS-guided choledochoduodenostomy (EUS-CDS) is a transluminal approach that creates a fistula between the duodenum and extrahepatic bile duct using a fully covered SEMS or lumen-apposing metal stents (LAMS)[68]. This biliodigestive anastomosis provides optimal palliation of MDBO; however it cannot be performed in cases of proximal obstruction or instances of gastric outlet obstruction where access to the duodenal bulb may be hindered[69]. A recent multicenter retrospective study compared EUS-CDS (n = 28) to PTBD (n = 58) and found that EUS-CDS was associated with higher clinical success (84.6% *vs* 62.1%, P = 0.04) with significantly lower rates of reintervention (10.7% *vs* 77.6%, P < 0.001)[70]. As a clinically effective technique (up to 96.2%), EUS-CDS has emerged as reliable alternative with acceptably low adverse events (10.5%)[71].

Recent studies have increasingly been using LAMS, which may be attributing to lower rates of stent malfunction. A large multicenter cohort in the United Kingdom and Ireland found that the technical success, clinical success, adverse events and reintervention rates using LAMS were 90.8%, 94.8%, 17.5%, and 8.3%, respectively[72]. Initially, plastic stents were used when EUS-CDS was first introduced. However, CSEMS quickly replaced plastic stents as a means to reduce bile leaks and stent occlusion[3] with significantly lower rates of adverse events (13.0% *vs* 42.8%, P = 0.01) and improved stent patency when compared to plastic stents[73-75]. At the moment the use of CSEMS *vs* LAMS varies from center to center. The large, tubular and rigid shape of CSEMS can theoretically increase the risk of stent migration [3]. In this context, LAMS were designed as a short, dumbbell shaped stents wit bilateral flanged ends which provide anti-migratory properties by anchoring across non-adherent lumens[3]. Further improvements were made with the development of an electrocautery-enhanced delivery system that enables a faster single step "free-hand" puncture which has led to high rates of technical success by eliminating the need for accessory changes[76]. However, two recent studies comparing LAMS *vs* SEMS found no differences in technical and clinical success or postprocedure related adverse events[77,78].

Intrahepatic approach

In instances of proximal malignant obstruction EUS-guided hepaticogastrostomy (EUS-HGS) creates a fistulized tract between the gastric wall and left intrahepatic duct. Its technical feasibility was first introduced in 2004 and since then it has become a widely used technique[79]. The European Society of Gastrointestinal Endoscopy recommends placement of partially or fully covered SEMS for drainage of malignant obstruction[68]. HGS can be performed where there is dilation of the left intrahepatic duct with segment III being the preferred puncture site[80]. There are a few contraindications to the procedure which include gastric wall tumor infiltration, large volume ascites, and coagulopathy[80,81]. Its role in hilar obstruction is reserved for specific cases as drainage from the left intrahepatic duct does not equate to drainage of a right sided obstruction[69]. A study described access from the proximal

duodenum to right intrahepatic duct (hepaticoduodenostomy) for cases of isolated right sided obstruction (with a technical success 100% and clinical success 83%)[82], but widespread use of this technique has not been adopted due to difficulty with scope positioning and proper identification of the duct[83].

In general, this intrahepatic approach has been favored for distal malignant biliary drainage. The HGS route is associated with a lower risk of bile leakage as the localized liver parenchyma around the fistula site can provide a tamponade effect[73]. A prospective randomized trial comparing HGS (n = 24) and CDS (n = 24) in MDBO following failed ERCP reported a higher clinical success rate in the HGS group (91% *vs* 77%) at the expense of slightly more adverse event rates (20.0% *vs* 12.5%)[84]. A multitude of studies have compared CDS and HGS approaches (Table 2)[64,84-95]. A meta-analysis of 10 studies comparing HGS (n = 208) and CDS (n = 226) found no difference in technical success (94.1% *vs* 93.7%), clinical success (88.5% *vs* 84.5%), or rates of adverse events[96].

Recently, a large single center study of 215 patients (130 malignant lesions, 85 benign lesions) undergoing transhepatic biliary drainage by one endoscopist showed that the HGS approach used in up to 90% of cases was technical and clinically effective with few instances of reintervention (17.4%) needed within the malignant cohort that survived > 6 mo[67]. In this study, the endoscopist preferred HGS over CDS to decrease the risk of bleeding, stent misdeployment and potential making pancreatic surgical resection more difficult[67,97]. Of note, a study of 23 patients with concomitant duodenal and biliary obstruction undergoing single session EUS-HGS and gastrojejunostomy found that one patient with pancreatic cancer underwent successful pancreaticoduodenectomy 168 days post-biliary drainage and the fistula remained in situ with no complications[98]. On the other hand, in a large multicenter study comparing HGS (n = 24) to CDS (n = 23), the authors preferred CDS as it takes advantage of the anatomical proximity between the duodenal bulb and extrahepatic duct, by which puncture can be easier with shorter procedure times and less guidewire manipulation[85]. Another large international study of 182 patients (95 HGS, 87 CDS) suggested that CDS was associated with being 4.5 times more likely to achieve longer stent patency at the expense of higher adverse events, which may influence decisions based on patients survival[86]. In light of advancements with oncologic care, the prospect of reduced long reintervention may steer one to use CDS, especially since reintervention is easier due to shorter stent size, cannulation and steering in the duodenum[83].

While both techniques have acceptable outcomes, there is still no clear choice. Yet tailoring the technique based on anatomical features, altered anatomy, duodenal stenosis and dilated bile ducts may help endoscopists choose the right route for each patient[57,99]. A novel individualized algorithm was proposed based on patient anatomy following failed ERCP where the authors suggested using cross-sectional imaging to determine if an intrahepatic or extrahepatic approach based on the presence or absence of intra-hepatic biliary tree dilation[99]. The algorithm favored an intrahepatic approach if possible as a means to preserve anatomy. Yet, if intrahepatic dilation was technically unsuccessful, they recommended converting to an extrahepatic approach. In their prospective cohort of 52 patients, there was a technical success rate of 96% (35 intrahepatic, 17 extrahepatic).

COMPARING ERCP AND EUS-BD FOR MANAGEMENT OF MALIGNANT BILIARY OBSTRUCTION

As detailed above, ERCP remains the first choice when treating malignant biliary obstruction. Its widespread use and high success rate, especially in expert hands, makes it an effective modality for biliary decompression. The application of EUS-BD as a rescue therapy has proven to be a reliable tool with high technical and clinical success rates with moderate adverse event rates. Furthermore, instances of SAA or duodenal invasion may preclude the use of ERCP, and EUS-BD has gained momentum as the preferred therapy (as opposed to PTBD).

There is growing interest in using EUS-BD as a potential first line approach. A multicenter retrospective study comparing ERCP (n = 104) to EUS-BD (n = 104) demonstrated similar rates of technical success (94% *vs* 93%) and adverse events (8.65% *vs* 8.65%); though 4.8% of the ERCP cohort experienced post-procedural pancreatitis[100]. EUS-BD does have an added benefit of shorter procedural times with the possibility of longer stent patency by avoiding the diseased bile duct in question[3,101]. Additionally, in cases of an indwelling gastroduodenal stent, EUS-BD has been proven as a technical and clinically superior option when compared to endoscopic transpapillary stenting[102]. A recent meta-analysis of 9 studies with 634 patients found no significant differences between technical and clinical success, though the EUS-BD cohort had fewer rates of reintervention[103].

ABLATION THERAPY OF THE BILE DUCT

The goals of palliative biliary drainage aim to improve obstructive symptoms and quality of life. Yet endoscopic biliary decompression may only provide temporary relief; hence, the ability to provide

Table 2 Comparative studies of endoscopic ultrasound guided hepaticogastrostomy and choledochoduodenostomy

Ref.	Study design, Country	Number of HGS *vs* CDS	Technical success CDS *vs* HGS, %	Clinical success HGS *vs* CDS, %	Adverse events, HGS *vs* CDS, %
Tyberg *et al*[86], 2022	Multicenter,International	95 *vs* 87	92% *vs* 92%, NS	86% *vs* 100%, NS	21% *vs* 26%, $P = 0.17$
Minaga *et al*[85], 2019	Multicenter, Japan	24 *vs* 23	87.5% *vs* 82.6%, $P = 0.028$	100% *vs* 94.7%, $P = 0.0475$	28.6% *vs* 21%, $P = 0.583$
Cho *et al*[94], 2017	Single Center, Korea	21 *vs* 33	100% *vs* 100%, NS	86% *vs* 100%, $P = 0.054$	19% *vs* 15%, NS
Amano *et al*[93], 2017	Single Center, Japan	9 *vs* 11	100% *vs* 100%, NS	100% *vs* 100%, NS	11% *vs* 18%, NS
Ogura *et al*[92], 2016	Single Center, Japan	26 *vs* 13	100% *vs* 100%	92% *vs* 100%, $P = 0.0497$	8% *vs* 46%, $P = 0.005$
Guo *et al*[91], 2016	Single Center, China	7 *vs* 14	100% *vs* 100%, NS	100% *vs* 100%, NS	14% *vs* 14%, NS
Khashab *et al*[90], 2016	Multicenter,International	61 *vs* 60	92% *vs* 93%, $P = 0.75$	82% *vs* 85%, $P = 0.64$	20% *vs* 13%, $P = 0.37$
Artifon *et al*[84], 2015	Single Center, Brazil	24 *vs* 25	96% *vs* 91%	88% *vs* 70%	20% *vs* 13%
Poincloux *et al*[64], 2015	Single Center, France	66 *vs* 26	94% *vs* 96.7%, NS	93.8% *vs* 93.1%, NS	15% *vs* 7.6%, NS
Kawakubo *et al*[88], 2014	Multicenter, Japan	20 *vs* 44	95% *vs* 95%, NS	95% *vs* 93%, NS	4% *vs* 15%, NS
Park *et al*[89], 2015	Multicenter, Korea	20 *vs* 12	100% *vs* 92%, $P > 0.99$	90% *vs* 92%, $P > 0.99$	25% *vs* 33%, $P = 0.044$
Prachayakul and Aswakul[87], 2013	Single Center, Thailand	15 *vs* 6	93% *vs* 100%, NS	93% *vs* 100%, NS	0% *vs* 33%, NS
Kim *et al*[95], 2012	Single Center, Retrospective	13 (9 CDS; 4 HGS)	100% *vs* 75%, NS	100% *vs* 50%, NS	22% *vs* 50%, NS

NS: Not significant; HGS: Hepaticogastrostomy; CDS: Choledochoduodenostomy.

supplemental biliary ablation as means to induce local tumor necrosis, optimize stent patency, palliate symptoms and possibly enhance long term survival have been investigated with photodynamic therapy (PDT) and radiofrequency ablation (RFA)[104].

Photodynamic therapy

PDT utilizes a photosensitizing agent (which is activated by laser light) to ablate tumor tissue *via* apoptosis, necrosis, and an immunomodulatory effect[105]. The porphyrin phototoxic substance is given intravenously 3-4 d prior to the procedure to allow for preferential accumulation in the malignant tissue-during this period patients are advised to stay in a darkened room to avoid an accidental inflammatory reaction in normal tissue if exposed to light[106,107]. Next a guidewire and catheter position the fiberoptic probe in the bile duct where laser light at certain wavelengths (typically 630 nm) trigger the photosensitizing agent for 750 sec to generate free oxygen radicals that destroy the tumor bed and/or stricture[106,108,109]. An added benefit to this local apoptotic and inflammatory cascade is that these light waves can refract to the proximal biliary tree which are often beyond reach of the guidewire[110]. Following PDT, a stent is often placed. This highly specialized technique is limited to a few centers.

PDT has been shown to improve overall survival, stent patency and quality of life in unresectable cholangiocarcinoma. A sentinel PDT study in 2003 prospectively randomized 20 patients to PDT plus biliary stenting and 19 with stenting alone, and found that the PDT significantly increased the median survival (493 d *vs* 98 d) while also improving quality of life and biliary drainage[111]. Similar findings of improved survival were also confirmed in another randomized trial[112]. Another retrospective comparative study of 48 patients with unresectable cholangiocarcinoma (19 PDT with stent versus 29 with biliary stent only) demonstrated a significant survival advantage (16.2 mo *vs* 7.4 mo) with only three adverse events related to skin phototoxicity that were treated with topical therapy[113]. The survival benefit of PDT plus stenting has been confirmed in three meta-analyses[114-116]. Of note, while one of these studies reported an improved survival rate favoring the PDT cohort (525 *vs* 146), the analysis was limited by its inclusion of endoscopically and percutaneous administration of PDT and/or biliary stents[116]. That being said all studies favored PDT's improved survival benefit, with a relatively low adverse event rate of 11% specific to phototoxic reactions (*i.e.*, blisters, erythema, and pruritis)[115]. In order to avoid such a reaction, it is recommended that patients avoid direct sunlight for 4-6 wk after the procedure[104].

In light of these favorable findings, additional studies have been pursued to characterize the potential benefits of stent patency and effect of combination systematic therapy. A retrospective of 33 patients with unresectable disease found that the PDT cohort ($n = 18$) had noticeable longer periods of stent patency (224 d *vs* 177 d, $P = 0.002$) by which the authors felt that PDT may induce tumor "remodeling" to lessen cholestasis and prolong biliary decompression[117]. A synergistic effect between PDT and

systematic chemotherapy has also been prospectively[118] and retrospectively confirmed to enhance overall survival[119,120]. In on such study, 96 patients with unresectable perihilar and distal CCA were stratified by treatment type where median overall survival was 20 mo, 15 mo, and 10 mo in the combination PDT plus chemotherapy (n = 36), PDT alone (n = 34), and chemotherapy alone (n = 26) groups, respectively[120].

These positive findings must also be analyzed in context of the limitations of PDT use. It is a complex and exceedingly expensive procedure that typically is only performed in highly specialized centers[2]. The phototoxic side effects may not acceptable to patients, especially since minimizing direct sunlight one month after the procedure could impair the quality of life in a patient with a potentially short life expectancy[110]. While the last author in this present review has pioneered early PDT studies, we feel that the lack of FDA approval of this therapy, in the biliary tree, has made this therapy very difficult to be offered outside of specialized centers.

Radiofrequency ablation therapy

RFA uses electromagnetic energy and high wave frequencies to deliver thermal energy to targeted tissues[121,122]. This localized thermal energy induces direct coagulative necrosis and an indirect localized inflammatory response and T-lymphocyte activation which have anti-tumor properties[110,122]. Intraductal RFA can be performed during a conventional ERCP where a RFA catheter can pass over the guidewire in order to place the bipolar probes upstream from the stricture site, whereby ablation is applied with 7-10 watts for 1-2 min bursts, along the length of the stricture[104,123]. Afterwards the bile duct is cleared with a balloon sweep to remove residual debris and necrotic tissue followed by placement of plastic or metal stent to maintain adequate drainge[104,123]. Of note, RFA can also be used with balloon enteroscopy-assisted ERCP[124] or an EUS-guided HGS approach[125,126].

The indication for endobiliary RFA is to improve stent patency and survival in cases of inoperable malignant strictures[106,123]. In 2011, a prospective pilot study analyzed the utility of RFA in 21 patients with unresectable malignant biliary obstruction, and found that biliary patency was maintained by 20 and 16 patients at 30 and 90 d, respectively with no adverse events related to RFA[127]. However, a subsequent single center retrospective study of 66 patients demonstrated no added benefit in prolonged stent patency when comparing metal stenting with RFA to stenting alone[128]. Of note, this study did not differentiate their findings based on the stent used. Another study found a significant improvement and durability of stricture diameter using plastic (n = 6) and metal stents (n = 14)[129]. As such, analyzing endobiliary RFA according to the type of stent used may allow for a better interpretation of stent patency; as etiology of recurrent biliary obstruction varies from sludge formation, migration and tumor ingrowth for plastic stents, covered SEMS and uncovered SEMS, respectively[123,130].

Plastic stents are often used if repeated RFA sessions are planned. Two recent RCTs have examined the stent patency of RFA and plastic stents with conflicting results[131,132]. In one study, of 65 patients (32 RFA plus plastic stent, 33 plastic stent alone), stent patency was significantly longer (6.8 mo *vs* 3.4 mo) with a higher survival time (13.2 mo *vs* 8.3 mo) favoring the RFA and plastic stent arm[133]. While the other RCT also reported a higher survival time (14.3 mo *vs* 9.2 mo) there was no significant difference in stent patency or jaundice control in either group[134]. One possible reason for the discrepancy is that in the first RCT by Yang *et al*[133] patients underwent stent exchange every 3 mo, while the study by Gao *et al*[134] only performed a stent exchange as clinical indicated. In our practice we offer systematic stents revision at three months interval.

The use of SEMS is largely depending on the patient's life expectancy and unresectability. Both uncovered and covered SEMS have been investigated with mixed results[131,132,135]. A retrospective [131] and RCT[132] examining USEMS, found no significant differences in stent patency. Meanwhile, a single center retrospective study using UCSEMS and CSEMS in a cohort of 31 patients favored the use of either stent with RFA with prolonged stent patency (220.0 d *vs* 106.5 d)[135]. One meta-analysis of nine studies with 505 patients demonstrated a favorable mean stent patency of 50.6 d with improved survival in those undergoing RFA with SEMS compared to SEMS alone[136]. However, these findings should be interpreted with caution as four of these studies used a percutaneous route for RFA. In this context, another meta-analysis of 263 patients undergoing endoscopic RFA showed that strictures improved by 3.5 mm when using RFA with a median stent patency of 7.6 mo[137]. Yet, the authors did not stratify their findings based on the type of stent used.

While the findings of stent patency and survival benefit are confounded by study heterogeneity and route of RFA, there is a likely benefit of stent patency and overall survival with RFA in malignant biliary obstruction. In fact a recent RCT found that a combination of oral 5-fluoouracil and RFA improved the median overall survival (16 mo *vs* 11 mo) and period of stent patency (6.6 mo *vs* 5.6 mo)[138]. With more wide spread use, developments of newly automatic temperature controlled RFA systems[139] and endoluminal devices[140] have produced favorable results pertaining to both stent patency and survival. Interestingly, RFA appears to be a relatively safe procedure with few instances of cholecystitis (10%), cholangitis (6.2%), and pancreatitis (2.1%) that did no differ significantly when compared to stenting alone[107,136].

Table 3 Comparing Photodynamic therapy to endobiliary radiofrequency ablation

Treatment type	Mechanism	Adverse events	Pros	Cons
Photodynamic therapy	Photosensitizing agent is given intravenously 3-4 d prior to accumulate in tissue; then, a fiberoptic probe is introduced to transmit laser light (approximately 630 nm)-apoptosis, necrosis, and immunomodulatory effect	Phototoxicity, erythema, pruritus, blistering, and diffuse pain	Light waves can refract to the proximal biliary tree, beyond the reach of the guidewire	Expensive; highly specialized equipment needed; decreased quality of life (avoid direct sunlight 4-6 wk after treatment); limited to high specialized centers; lack of FDA approval
Endobiliary radiofrequency ablation	High frequency electromagnetic energy-cell death *via* thermal energy, coagulative necrosis, and indirect anti-tumor lymphocyte activation	Pancreatitis, cholecystitis, cholangitis hemobilia, abdominal pain	Widely available	Lack of standardization; potentially need > 1 session; can only be performed under fluoroscopy

Only a handful of studies have directly compared RFA to PDT (Table 3). One retrospective study found no statistically significant difference in the survival benefit between RFA (n = 16) and PDT (n = 32) in their cohort of unresectable cholangiocarcinoma (9.6 mo *vs* 7.5 mo)[141]. However, the other retrospective study showed that RFA was associated with better short-term effects (*i.e.*, reduction in bilirubin with fewer unplanned stent replacements)[142]. A recent meta-analysis of 55 studies comparing PDT (n = 1149), RFA (n = 545), and stent-only strategy (n = 452) found that PDT was associated with an improved overall survival rate (11.9 mo *vs* 8.1 mo *vs* 6.7 mo, respectively) and decreased 30-d mortality (3.3% *vs* 7.0% *vs* 4.9%, respectively)[143]. Though PDT did display higher rates of cholangitis (23.4% *vs* 9.5%) and liver abscess (4.9% *vs* 2.6%) when compared to RFA. The authors felt that RFA may be favored in the setting of lower adverse events, decreased costs (Photofrin dose $37000 *vs* RFA catheter $1200) and similar lengths of stent patency (PDT 6.1 mo *vs* RFA 5.5 mo).

CONCLUSION

In conclusion, the optimal palliation of malignant obstruction remains a challenging task for endoscopists and requires a dedicated team able to offer a variety of intervention based on patient presentation, symptoms and expected survival.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Gastric intestinal metaplasia development in African American predominant United States population

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Abstract

BACKGROUND

Gastric cancer significantly contributes to cancer mortality globally. Gastric intestinal metaplasia (GIM) is a stage in the Correa cascade and a premalignant lesion of gastric cancer. The natural history of GIM formation and progression over time is not fully understood. Currently, there are no clear guidelines on GIM surveillance or management in the United States.

AIM

To investigate factors associated with GIM development over time in African American-predominant study population.

METHODS

This is a retrospective longitudinal study in a single tertiary hospital in Washington DC. We retrieved upper esophagogastroduodenoscopies (EGDs) with gastric biopsies from the pathology department database from January 2015 to December 2020. Patients included in the study had undergone two or more EGDs

with gastric biopsy. Patients with no GIM at baseline were followed up until they developed GIM or until the last available EGD. Exclusion criteria consisted of patients age < 18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. The study population was divided into two groups based on GIM status. Univariate and multivariate Cox regression was used to estimate the hazard induced by patient demographics, EGD findings, and *Helicobacter pylori* (*H. pylori*) status on the GIM status.

RESULTS

Of 2375 patients who had at least 1 EGD with gastric biopsy, 579 patients were included in the study. 138 patients developed GIM during the study follow-up period of 1087 d on average, compared to 857 d in patients without GIM ($P = 0.247$). The average age of GIM group was 64 years compared to 56 years in the non-GIM group ($P < 0.001$). In the GIM group, adding one year to the age increases the risk for GIM formation by 4% ($P < 0.001$). Over time, African Americans, Hispanic, and other ethnicities/races had an increased risk of GIM compared to Caucasians with a hazard ratio (HR) of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. No gender difference was observed between the study populations. Gastritis was associated with an increased risk for GIM development with an HR of 1.62 (1.07, 2.44). On the other hand, *H. pylori* infection did not increase the risk for GIM.

CONCLUSION

An increase in age and non-Caucasian race/ethnicity are associated with an increased risk of GIM formation. The effect of *H. pylori* on GIM is limited in low prevalence areas.

Key Words: Gastric intestinal metaplasia; Gastric cancer; *Helicobacter pylori*; Retrospective longitudinal study; Esophagogastroduodenoscopy; African American population

Core Tip: Gastric intestinal metaplasia (GIM) is a precancerous lesion, and previous literature showed a higher rate in the United States minorities. Our study highlighted the natural history of GIM over time. It was observed in the study that irrespective of being minorities, Non-Caucasian races/ethnicities have a higher risk for GIM. Gastritis and older age contribute to GIM formation. The effect of *Helicobacter pylori* infection was not significant in our population.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer mortality worldwide[1,2]. Non-cardiac intestinal-type gastric adenocarcinoma represents the majority of cases in the United States[2]. In 2018, over 26000 new cases of gastric cancer were reported with 10600 deaths in the United States[3]; in 2020, more than 700000 deaths were reported globally[4]. The high mortality rate of gastric cancer is mostly attributed to the late presentation of the disease. In areas with a high incidence of gastric cancer, the mortality-incidence ratio is decreased by screening programs[1], while in areas with low incidence, surveillance programs for gastric premalignant lesions in high-risk individuals are likely an optimal screening strategy based on risk stratification.

The Correa cascade proposed that intestinal-type gastric adenocarcinoma is formed from normal gastric mucosa that progresses through a series of transition stages: Chronic gastritis, atrophic gastritis, gastric intestinal metaplasia (GIM), and dysplasia, which can progress to gastric adenocarcinoma[5,6]. The latter three histopathological findings are considered as gastric premalignant lesions. GIM is defined as the replacement of normal gastric epithelium with intestinal epithelium consisting of Paneth, goblet, and absorptive cells[7]. The replacement happens under chronic stressors like inflammation. The prevalence of GIM in the general United States population is estimated to be 5%-8%[7] with an 0.13%–0.25%[6,7] estimated annual risk of progression into gastric cancer and a median time to

progression of around 6 years[6].

Currently, GIM is more recognized as the best pre-malignant stage for surveillance because identifying and treating these lesions can potentially prevent further progression to gastric cancer[2,5]. Multiple international guidelines recommend surveillance for gastric pre-malignant lesions including GIM[8,9]; on the contrary, the American Gastroenterology Association (AGA) recommends against such screening guidelines for GIM with some exceptions[2]. Multiple risk factors have been identified to help guide surveillance including smoking, alcohol use, ethnicity, family history of gastric cancer, and genetic factors[10]. However, long-term effect of surveillance is not well understood in countries with a low incidence of gastric cancer due to the limitation of the available studies. Furthermore, the lack of clear guidelines for GIM medical management after diagnosis has added to the challenge[2]. Thus, we designed this retrospective longitudinal study to investigate potential risk factors involved in GIM formation from normal mucosa in an African American predominant United States population.

MATERIALS AND METHODS

Study design

This is a retrospective longitudinal study conducted at Medstar Washington Hospital Center. The study was reviewed and approved by the Medstar Health Research Institute and Georgetown University Hospital Institutional Review Board.

Study population

Patients with GIM were identified from the Pathology Department's database at Medstar Washington Hospital Center. Patients included in the study had undergone two or more esophagogastroduodenoscopies (EGDs) with gastric biopsy, with at least one EGD performed between January 2015 to December 2020. Exclusion criteria consisted of patients age < 18, pregnancy, previous diagnosis of gastric cancer, and missing data including pathology results or endoscopy reports. Patients with a baseline of no GIM were followed up longitudinally. The follow-up period ended at the event occurrence (GIM formation) or the last follow-up EGD. Based on the GIM status from the gastric biopsy at the end of the follow-up period, the study population was divided into two groups–GIM group and non-GIM group. Patients were excluded from the study if they were younger than 18 years old.

Data collection

Electronic medical records were reviewed to collect and analyze the following patient information: Demographics, medication use, EGDs findings, *Helicobacter pylori* (*H. pylori*) status, gastric biopsy reports, and laboratory findings. Patients' *H. pylori* statuses were exclusively based on biopsy testing.

Data analysis

To present the data, we used frequency with percentage for categorical variables and median with first and third quartile (IQR) for non-normal continuous variables. The D'Agostino-Pearson test was used to test normality. Chi-square test with Yate's correction or Kruskal-Wallis rank-sum test was performed to compare the difference between the groups. Kaplan-Meier estimators were calculated, and the curves were plotted to show the probability of GIM at a respective time interval after the baseline. To detect the differences in survival, we used Peto-Peto's weighted Log-rank test. Univariate and multivariate Cox proportional hazards regression model was performed to investigate how the predictors were associated with the risk of GIM over time. All unadjusted and adjusted hazard ratios with 95 percent confidence intervals were presented, along with the unadjusted *P* values. Statistical significance was set at a *P* value less than 0.05 and all statistical analyses were conducted with R software. The statistical methods of this study were reviewed by Jiling Chou from MedStar Health Research institute.

RESULTS

Overall data summary

Of 2375 patients who had at least 1 EGD with gastric biopsy during 2015 to 2020, 579 patients met our inclusion criteria. A total of 138 (23.8%) patients developed GIM during the follow-up period of 1087 days on average, compared to 857 d in patients without GIM ($P = 0.247$). The GIM group was older with an average age of 64 years compared to 56 years in the non-GIM group ($P < 0.001$). Female patients represented 60.7% (351 patients) of the total study population and there was not a significant difference between study groups ($P = 0.208$). Ethnicity was significantly different between the study groups ($P = 0.032$): African American, Caucasian, Hispanic and other ethnicities/races represented 72.9% (94 patients), 9.3% (12 patients), 5.4% (7 patients), and 12.4% (16 patients) of the GIM group respectively, compared to 71% (287 patients), 18.1% (73 patients), 2.7% (11 patients), and 8.2% (33 patients) in the non-GIM group respectively (Table 1).

Table 1 Data summary and comparison between patients with and without gastric intestinal metaplasia

Level		Baseline no GIM			
		Overall	No GIM	GIM	*P* value
		579	441	138	
Follow-up days [median (IQR)]		885.0 (257.5, 1901.5)	857.0 (259.0, 1834.0)	1087.0 (260.5, 2307.3)	0.247
Age baseline [median (IQR)]		58.0 (49.0, 67.8)	56.0 (46.8, 65.0)	64.00 (54.0, 72.0)	< 0.001
Sex (%)	Male	227 (39.3)	166 (37.7)	61 (44.2)	0.208
	Female	351 (60.7)	274 (62.3)	77 (55.8)	
Ethnicity/Race (%)	Caucasian	85 (15.9)	73 (18.1)	12 (9.3)	0.032
	AA	381 (71.5)	287 (71.0)	94 (72.9)	
	Hispanic	18 (3.4)	11 (2.7)	7 (5.4)	
	Other	49 (9.2)	33 (8.2)	16 (12.4)	
Obesity (%)	BMI < 30	261 (56.7)	191 (53.5)	70 (68.0)	0.013
	BMI > 30	199 (43.3)	166 (46.5)	33 (32.0)	
Smoking status (%)	Never	269 (54.8)	207 (55.3)	62 (53.0)	0.198
	Previous	119 (24.2)	84 (22.5)	35 (29.9)	
	Current	103 (21.0)	83 (22.2)	20 (17.1)	
Biopsy site (%)	≤ 2	227 (39.2)	190 (43.1)	37 (26.8)	0.001
	> 3	352 (60.8)	251 (56.9)	101 (73.2)	
H. pylori at Baseline (%)	No	499 (86.2)	382 (86.6)	117 (84.8)	0.686
	Yes	80 (13.8)	59 (13.4)	21 (15.2)	
H. pylori at follow-up (%)	No	536 (92.6)	413 (93.7)	123 (89.1)	0.114
	Yes	43 (7.4)	28 (6.3)	15 (10.9)	
n		80	59	21	
H. pylori at follow up with positive Baseline (%)	No	65 (81.2)	48 (81.4)	17 (81.0)	1
	Yes	15 (18.8)	11 (18.6)	4 (19.0)	
Gastritis (%)	No	209 (36.1)	180 (40.8)	29 (21.0)	< 0.001
	Yes	370 (63.9)	261 (59.2)	109 (79.0)	
Ulcer (%)	No	534 (92.2)	408 (92.5)	126 (91.3)	0.778
	Yes	45 (7.8)	33 (7.5)	12 (8.7)	
81 mg Aspirin Use at Baseline (%)	No	450 (77.7)	347 (78.7)	103 (74.6)	0.379
	Yes	129 (22.3)	94 (21.3)	35 (25.4)	
81 mg Aspirin use at follow up (%)	No	453 (78.2)	359 (81.4)	94 (68.1)	0.001
	Yes	126 (21.8)	82 (18.6)	44 (31.9)	
PPI usage at baseline (%)	No	392 (67.7)	285 (64.6)	107 (77.5)	0.006
	Yes	187 (32.3)	156 (35.4)	31 (22.5)	
PPI usage at follow up (%)	No	318 (54.9)	233 (52.8)	85 (61.6)	0.088
	Yes	261 (45.1)	208 (47.2)	53 (38.4)	
Blood type (%)	A	72 (31.2)	47 (28.7)	25 (37.3)	0.317
	B	42 (18.2)	28 (17.1)	14 (20.9)	
	O	109 (47.2)	82 (50.0)	27 (40.3)	
	AB	8 (3.5)	7 (4.3)	1 (1.5)	
Hemoglobin [median (IQR)]		11.2 (9.2, 12.8)	11.5 (9.5, 13.0)	10.5 (9.0, 12.2)	0.075

Hemoglobin Baseline [median (IQR)]	10.8 (9.2, 12.8)	11.8 (9.7, 13.1)	9.60 (8.40, 11.00)	< 0.001

GIM: Gastric intestinal metaplasia; IQR: Interquartile range; AA: African Americans; BMI: Body mass index; PPI: Proton pump inhibitors.

Regarding medication use, a higher percentage of the GIM group [44 patients (31.9%)] was using 81 mg of aspirin on follow-up, compared to 82 patients (18.6%) in the non-GIM group (P = 0.001). A lower percentage of the GIM group [31 patients (22.5 %)] was using proton pump inhibitors (PPI) at baseline compared to 156 patients (35.4%) in the non-GIM group (P = 0.006). However, aspirin use at baseline and PPI use on follow up was not significantly different between study groups.

On follow-up EGDs, gastritis was observed more in the GIM group [109 patients (79.0 %)] compared to 261 patients (59.2%) with gastritis in the non-GIM group (P < 0.001) (Table 1).

H. pylori was positive in the baseline biopsies of 80 patients (13.2%), compared to those of 43 patients (7.4 %) on follow-up. Of this *H. pylori* positive group, 15 patients had positive *H. pylori* at both the baseline and follow-up, but this persistent *H. pylori* infection was not different between the two study groups. A detailed summary of the data is presented in Table 1.

Risk of GIM over time

In a group of patients with no GIM at baseline, adding one year in age increases the risk of GIM by 4% over time with a P value < 0.001. In comparison to the age group of 45 years or younger, patients have a hazard ratio (HR) of 2.13 (P = 0.028), 2.09 (P = 0.029), and 4.03 (P < 0.001) for age groups 46-55, 56-64, and ≥ 65 years respectively. Over time, African Americans, Hispanics, and other ethnicities/races had an increased risk of GIM compared to Caucasians with an HR of 2.12 (1.16, 3.87), 2.79 (1.09, 7.13), and 3.19 (1.5, 6.76) respectively. Gastritis on follow-up biopsy was associated with a higher risk of GIM with an HR of 1.62 (1.07, 2.44) (P = 0.022), while 81 mg aspirin use increased the risk of GIM by 49% (P = 0.031). Obesity at baseline had a 42% less risk of GIM (P = 0.010). Using the *H. pylori*-negative group at baseline and follow-up as a reference group, *H. pylori* infection at baseline or follow-up, as well as the persistence of *H. pylori* infection did not have significant effects on GIM risk over time. Subgroup analysis of patients with *H. pylori* present at baseline shows no major difference from the main study analysis (Table 2).

On multivariate Cox regression analysis, the age ≥ 65 group was continuously associated with a higher risk of GIM with an HR of 3.01 (P = 0.014). African Americans and other ethnicities have a higher risk of GIM with an HR of 3.4 (P = 0.026) and 7.46 (P = 0.001) when compared to Caucasians respectively. Hispanic, other age groups, gastritis, *H. pylori* status, and smoking status did not reach the level of statistical significance on multivariate analysis (Table 3).

We calculated the Kaplan-Meier survival estimate for GIM development over 12 years. The population at risk is limited by the available follow-up EGD and censored observations. At the 12 years follow-up, 26 patients were at GIM risk (Figure 1A). Close to 50% of the population at risk developed GIM during 12 years of follow-up. A 12 years survival Curve was done to present the survival probability of developing GIM based on ethnicity, age group, and gastritis status (Figure 1B-D). We observed a significant difference in the GIM development over 12 years based on gastritis status (P = 0.023), age group (P < 0.0001), and ethnicity (P = 0.023).

DISCUSSION

GIM is a recognized gastric pre-malignant lesion with an increased risk for developing gastric cancer. The risk factors for GIM formation and evolution are significant clinical interest and thus currently under active investigation since these factors will likely help design optimal surveillance programs and management of GIM after diagnosis. Our study showed that the GIM group was older compared to the non-GIM group (Table 1). In multiple studies including ours, more advanced age was associated with an increased risk of GIM formation, progression, and gastric cancer development, which could be attributable to prolonged exposure of gastric mucosa to mutagenic factors and inflammation[1,4,11]. The average age at GIM diagnosis in low gastric cancer incident countries was 60 to 67 years, comparable to the average age of 64 in our GIM group (Table 1)[1,11,12]. A one-year increase in age was associated with a 4% increase in GIM risk in our population. Age groups of 45-54, 55-64, and > 65 were associated with an increased risk for GIM development compared to the < 45 age group (Table 2). The age group > 65 had the highest HR, and it was the only age group associated with an increased risk of GIM formation on multivariate analysis (Table 3). However, a study in China found that age > 45 is associated with GIM progression[13]. After five years of follow-up, around 50% of patients in group > 65 develop GIM, compared to 10% in < 45 age group (Figure 1C). These results suggest that an age close to 65 may be a good threshold for screening for GIM.

Although gastric cancer is known to be more common in males[14], GIM has equally affected both genders in our study and others[1,4]. In contrast, a cohort study in Puerto Rico showed a greater

Table 2 Univariate Cox proportional hazards regression model results for gastric intestinal metaplasia formation over time

Predictor	GIM	
	HR (95%CI)	*P* value
Age	1.04 (1.02, 1.05)	< 0.001
Age (ref: ≤ 45)		
46-55	2.13 (1.08, 4.19)	0.028
56-65	2.09 (1.08, 4.03)	0.029
> 65	4.03 (2.17, 7.48)	< 0.001
Female	0.81 (0.58, 1.14)	0.229
Race/Ethnicity (ref: Caucasians)		
African American	2.12 (1.16, 3.87)	0.015
Hispanic	2.79 (1.09, 7.13)	0.032
Other	3.19 (1.50, 6.76)	0.003
Obesity (BMI > 30)	0.58 (0.38, 0.88)	0.010
Gastritis	1.62 (1.07, 2.44)	0.022
***H. pylori* (ref: Baseline: Neg, follow-up: Neg)**		
Baseline: Neg, follow-up: Pos	0.88 (0.45, 1.7)	0.695
Baseline: Pos, follow-up: Neg	1.16 (0.7, 1.94)	0.563
Baseline: Pos, follow-up: Pos	1.02 (0.37, 2.8)	0.966
PPI Usage at follow-up	0.81 (0.57, 1.14)	0.225
PPI Usage Baseline	0.80 (0.54, 1.20)	0.280
Aspirin Use at follow-up (81 mg)	1.49 (1.04, 2.14)	0.031
Aspirin Use Baseline (81 mg)	1.45 (0.98, 2.13)	0.063
Smoking status (ref: Never)		
Previous smoker	1.35 (0.89, 2.04)	0.161
Current smoker	1.01 (0.61, 1.68)	0.972
Blood group (ref: Group A)		
Blood group B	1.07 (0.56, 2.07)	0.835
Blood group O	0.66 (0.38, 1.14)	0.135
Blood group AB	0.24 (0.03, 1.77)	0.161
Haemoglobin level at follow-up	1.00 (0.92, 1.09)	0.962
Haemoglobin level at baseline	0.83 (0.74, 0.93)	0.001

GIM: Gastric intestinal metaplasia; HR: Hazard ratio; BMI: Body mass index; PPI: Proton pump inhibitors; Neg: Negative; Pos: Positive.

percentage of females affected by GIM compared to males[12], and in a Thai population, the male sex was a risk factor for GIM development[11]. The influence of gender on GIM development might be significant, but our study might have failed to detect it due to the small sample size. Alternatively, gender might have an isolated effect on GIM progression to gastric cancer rather than GIM development.

Non-cardia gastric cancer has a higher incidence rate in certain United States race/ethnicity minorities including, African Americans, Hispanics, and Asians[15]. Previous studies on the United States population have shown that ethnicity is a risk factor for GIM formation, independent of age or *H. pylori* status[16-18]. Non-Hispanic whites have the lowest risk of GIM in comparison to other races/ethnicities. Hispanics, followed by African Americans, carry the highest risk for GIM compared to non-Hispanic whites, which is consistent with other studies[16-18]. Our study also showed African Americans, Hispanics, and other ethnicities/races had an increased risk of GIM compared to Caucasians (Table 2). However, the Hispanic population did not reach the statistical significance level on mult-

Table 3 Multivariate Cox proportional hazards regression model results for gastric intestinal metaplasia formation over time

	HR (95%CI)	*P* value
Age at baseline (ref: ≤ 45)		
46-55	1.75 (0.67, 4.58)	0.255
56-65	1.44 (0.56, 3.68)	0.445
> 65	3.01 (1.25, 7.26)	0.014
Female	0.8 (0.48, 1.33)	0.384
Race/Ethnicity (ref: Caucasians)		
African American	3.4 (1.16, 9.95)	0.026
Hispanic	1.64 (0.28, 9.47)	0.582
Other	7.46 (2.26, 24.67)	0.001
Obesity (BMI > 30)	0.71 (0.42, 1.2)	0.201
Gastritis	1.65 (0.97, 2.81)	0.065
***H. pylori* (ref: Baseline: Neg, follow-up: Neg)**		
Baseline: Neg, follow-up: Pos	1.26 (0.53, 2.98)	0.602
Baseline: Pos, follow-up: Neg	0.6 (0.26, 1.37)	0.223
Baseline: Pos, follow-up: Pos	1.13 (0.34, 3.76)	0.847
Smoking (ref: Never)		
Previous	0.96 (0.56, 1.65)	0.876
Current	0.74 (0.38, 1.47)	0.398

HR: Hazard ratio; BMI: Body mass index; Neg: Negative; Pos: Positive.

ivariant analysis, likely due to the small size of Hispanic population in our study (Table 3). The Asian population is also thought to have a higher risk of GIM, but this population is generally less investigated in United States literature due to the small number of Asians in the United States. Asian and different groups of ethnic and racial minorities were combined as the other ethnic/racial group in our study, this group carried the highest HR when compared to Caucasians. After 5 years of follow-up, close to 25% and 50% of Caucasians and other ethnic/racial groups developed GIM (Figure 1B). Our study is notable that African Americans represent the majority of our study population and carry a higher risk for GIM.

Currently, the AGA recommends surveillance for ethnic/racial minorities only on a conditional basis [2]. Place of birth, rather than ethnicity, was shown to be a risk factor for GIM in one study, where only Hispanics born outside the United States carry a higher risk for GIM compared to Hispanics born in the United States regardless of *H. pylori* status[19]. The effect of place of birth and race on GIM needs further investigation, as it might be a potential factor that affects surveillance.

The impact of *H. pylori* infection on GIM formation and progression was extensively investigated, but the results in the literature were often conflicting thus suggesting the complex role of *H. pylori* in GIM and gastric cancer. *H. pylori* infection is thought to affect the development and progression of GIM[20], but few studies have shown either formation or progression but not both[17]. Ethnicity, genetic makeup, and *H. pylori* virulence factors are additional factors that can further influence the effect of *H. pylori* on GIM[10,18,21]. However, in the present study, no clear effect of *H. pylori* on GIM development was found as shown in other studies[4,19,22]. In our study population, only 13.8% of patients had *H. pylori* infection, which is lower than the reported average *H. pylori* infection in the United States and patients with positive *H. pylori* infection at baseline biopsy, follow-up biopsy, or both seem to have the same risk of developing GIM, not different from those who tested negative for *H. pylori*. However, given the known strong association between *H. pylori* and gastric cancer, we agree with the AGA recommendation for testing and treating *H. pylori* and confirming its eradication, especially if positive in GIM, even though our results did not show a direct effect of *H. pylori* on GIM formation.

Chronic gastritis is part of the Correa cascade, and it precedes GIM development. The long-term effect of *H. pylori*-negative chronic gastritis and its role in the development of GIM have been poorly studied. A prospective study in Thailand investigated 400 patients with chronic gastritis and showed that chronic gastritis is associated with an increased risk for progression regardless of *H. pylori* status[4]. Our study showed that gastritis is associated with GIM formation over time. The gastric inflammation,

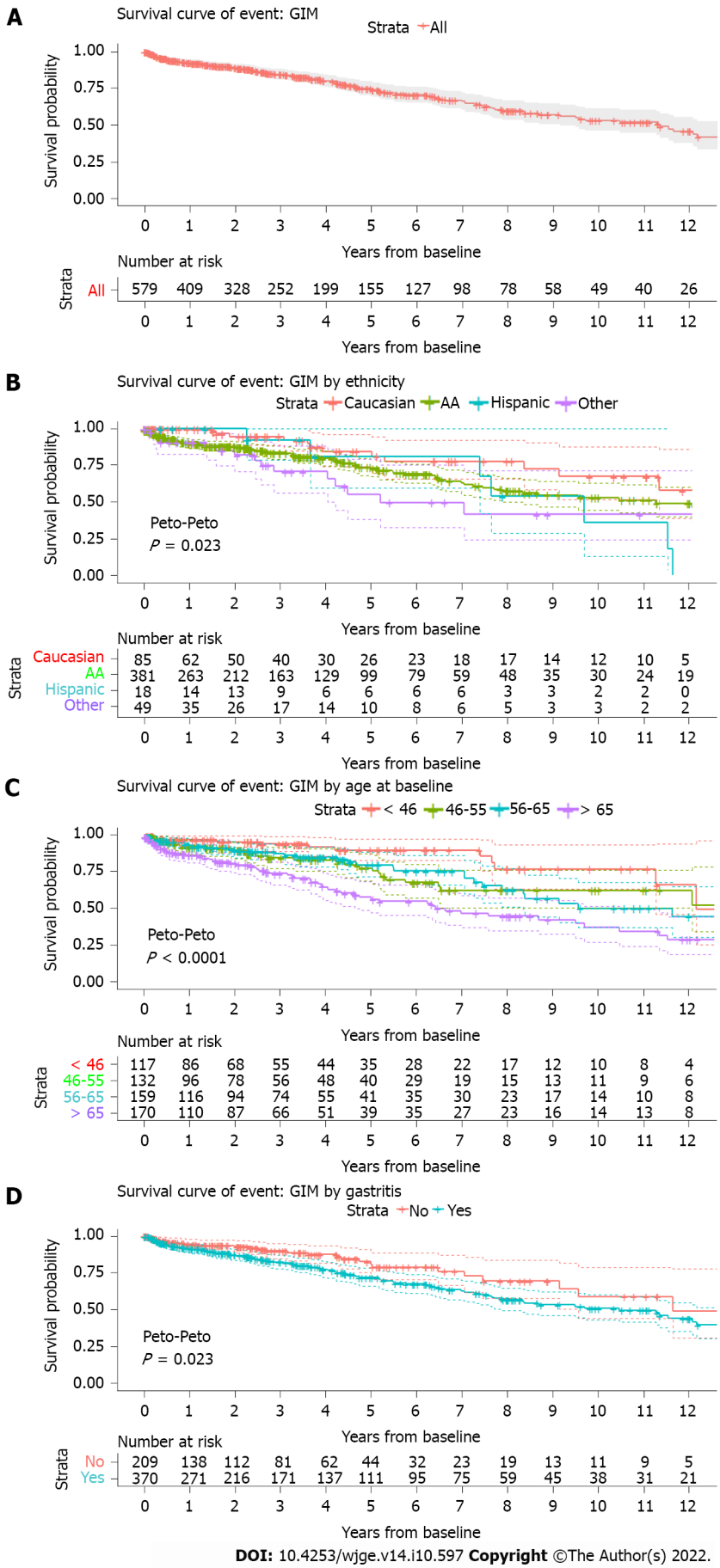

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Figure 1 Survival estimate curve along with population at risk table. A: Estimated probability of not developing gastric intestinal metaplasia at a

respective time interval after baseline without gastric intestinal metaplasia (GIM); B: The estimated probability of not developing gastric intestinal metaplasia in different ethnicities/races at a respective time interval after baseline without GIM; C: The estimated probability of not developing gastric intestinal metaplasia in different age groups at a respective time interval after baseline without GIM; D: The estimated probability of not developing gastric intestinal metaplasia in gastritis compared to no gastritis at a respective time interval after baseline without GIM. GIM: Gastric intestinal metaplasia.

rather than the *H. pylori* infection itself, might be driving GIM formation. On the 12 years survival curve, a significant difference in GIM formation is shown between the group with and without gastritis, noticeable as early as 1 year (Figure 1D). Thus, early recognition and treatment of gastritis can impact GIM formation and possibly prevent GIM thus reducing gastric cancer risk.

The study is limited by its retrospective nature. All the patients in the study are from a single tertiary center in Washington, DC. The standard evaluation of GIM in our pathology lab does not involve further grading or classification, which added to the study's limitation. In spite of the retrospective nature of the study, the strength of our study is its unique study design and distinct study population to assess the longitudinal data over time between upper endoscopies in a single academic center with a predominantly African American population, which has not been adequately investigated in other studies. It is also notable that this study population has a low prevalence of *H. pylori*, thus allowing us to examine other risk factors involved in the development of GIM aside from *H. pylori* infection. Our limitations also include the low number of Asians in our study population who were included as the other ethnic/racial category in our study, thus limiting comparisons with other published studies from Asia.

CONCLUSION

In conclusion, our study demonstrates that race is an important risk factor for GIM and ethnic/racial minorities in the United States carry a higher risk of GIM compared to Caucasians. Older age, especially age group > 65, was associated with higher GIM risk. Gastritis rather than *H. pylori* infection is also associated with GIM formation in our low *H. pylori* prevalent patient population. These risk factors identified in our study will serve as important components in developing risk stratification models for optimal surveillance programs for GIM and gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Gastric intestinal metaplasia (GIM) is a form of gastric pre-malignant lesions. It falls on the spectrum of the Correa cascade. The cascade includes chronic gastritis, atrophic gastritis, GIM, and dysplasia.

Research motivation

We designed this study to investigate factors leading to GIM formation. There is a lack of literature about this topic in the United States, especially among ethnic minorities, which are considered high-risk populations.

Research objectives

We aimed to identify factors that increase GIM formation in high-risk populations. These factors would help guide the future surveillance of selected patients and possibly suggest treatment modalities.

Research methods

This is a retrospective longitudinal study in a tertiary hospital in Washington, DC. The study includes patients with at least two upper endoscopies with gastric biopsies to assess the evolution of GIM over time. A Cox regression model was built to investigate the significant factors over the study time.

Research results

Our study confirms that Ethnicity-Race minorities have a higher rate of GIM formation. We found that gastritis increases GIM formation over time. *Helicobacter pylori* in low-prevalence areas might not be a strong risk factor. Our results emphasize on future surveillance of minorities and management of gastritis as a way to reduce the burden of gastric cancer.

Research conclusions

In conclusion, our study suggests that older age, having gastritis, or being from ethnic-race minorities is associated with an increased risk of GIM.

Research perspectives

Further studies are needed to clarify factors associated with GIM progression and regression. This would help form a complete picture of the development and progression of gastric pre-malignant lesions.

FOOTNOTES

Author contributions: Ahmad AI and Cho W contributed to the study designing and wrote the manuscript; Ahmad AI, Cho W, Lee A and Pothoulakis I contributed to the manuscript edit; Lee A, Caplan C, Wikholm C performed the project coordinator; Lee A, Caplan C, Almothafer Z, Raval N, Marshall S, Hodgins N, Kang IG, Chang RK, Dailey Z, Daneshmand A, Kapadia A, Oh JH, Rodriguez B, Sehgal A, Sweeney M, Swisher CB, Childers DF, Mishra A, O'Connor C and Sequeira LM contributed to the data collection.

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SYSTEMATIC REVIEWS

Water-jet *vs* traditional triangular tip knife in peroral endoscopic myotomy for esophageal dysmotility: A systemic review and meta-analysis

Yuliya Belopolsky, Srinivas R Puli

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Abstract

BACKGROUND

Peroral endoscopic myotomy is an increasingly used less invasive modality to treat esophageal dysmotility. Recently, triangular tip knife with integrated water jet function has been introduced to mitigate multiple instrument exchanges.

AIM

To compare traditional triangular tip knife and water jet knife in terms of procedural success, duration, instrument exchanges, coagulation forceps use, and adverse events.

METHODS

We conducted a systemic review and meta-analysis with two authors independently in electronic databases (PubMed, Embase, and Cochrane Library) from inception through May 2021. In addition, we conducted a relevant search by *Reference Citation Analysis* (RCA) (https://www.referencecitationanalysis.com). A fixed-effects model was used to calculate weighted mean, odds ratio (OR), and confidence intervals (CI).

RESULTS

We included 7 studies involving 558 patients. Triangular knife and water jet knife were similar in odds of procedural success with ratio of 4.78 (95%CI = 0.22-102.47) and odds of clinical success with ratio of 0.93 (95%CI = 0.29-2.97), respectively. Water jet knife had fewer instrument exchanges compared to triangular knife (2.21, 95%CI = 1.98-2.45 *vs* 11.9, 95%CI = 11.15-12.70) and usage of coagulation forceps (1.75, 95%CI = 1.52-1.97 *vs* 2.63, 95%CI = 2.37-2.89). Adverse events were higher in triangular knife group (OR: 2.30, 95%CI = 1.35-3.95).

CONCLUSION

Peroral endoscopic myotomy using water jet knife is comparable in terms of pro-

cedural success to triangular tip knife. Water jet knife also required shorter procedural duration, less instrument exchanges, coagulation devices, and overall adverse events.

Key Words: Gastroenterology; Endoscopy gastrointestinal; Esophageal motility disorders; Water jet knife; Dysmotility

Core Tip: Peroral endoscopic myotomy (POEM) has gained traction due to its novel technique of preserving the mucosal layer while working in the submucosa and minimizing risk of leakage of contents into the mediastinum. It hails comparable efficacy and safety data to the standard surgical therapy of laparoscopic Heller myotomy in short term follow up studies. The major steps of POEM are similar among centers, including small mucosal incision, submucosal tunneling, myotomy, and mucosal closure. Within these individual steps, many tools and variations exist to achieve the result. Recently, an innovative water-jet integrated triangular tip knife (WJ) has been devised in order to improve procedural time with less instrument changes, as well as minimize adverse events. There have been several studies comparing the conventional triangular tip knife and WJ and suggesting that WJ can achieve similar clinical and procedural success rate, but with lower adverse effects, instrument changes, and intra-procedural coagulation devices. This is the first meta-analysis to compare the two instruments.

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INTRODUCTION

Idiopathic achalasia is classified as an esophageal motility disorder thought to be related to loss of inhibitory ganglion cells in the esophageal myenteric plexus. This leads to failure of the lower esophageal sphincter (LES) to relax and aperistalsis of the esophageal body[1]. It has an annual incidence of 1 in 100000 and a prevalence of about 10 in 100000[2]. At present-day, there are no curative treatments to reverse loss of neurons, and thus palliative therapies to weaken the LES and allow passive emptying of the esophagus have been implemented. These have ranged from endoscopic pneumatic dilation to invasive measures such as surgical myotomy.

More recently, peroral endoscopic myotomy (POEM) has gained traction due to its novel technique of preserving the mucosal layer while working in the submucosa and minimizing risk of leakage of contents into the mediastinum. It hails comparable efficacy and safety data to the standard surgical therapy of laparoscopic Heller myotomy in short term follow up studies[3,4]. The first endoscopic myotomy was described in 1980 by three Venezuelan gastroenterologists, and later the technique refined with a submucosal tunnel based on two USA publications in 2007 performed on pigs[5-7]. POEM as we know it today, was initially performed on 17 achalasia patients by Inoue *et al*[8] in a groundbreaking study in 2010.

The major steps of POEM are similar among centers, including small mucosal incision, submucosal tunneling, myotomy, and mucosal closure. Within these individual steps, many tools and variations exist to achieve the result. Traditionally, the knife that has been used is a conventional triangular tip knife (TT), which is an electrosurgical knife that has a conductive triangle tip for cutting mucosa. Cutting mucosa can be performed in any direction without rotating the knife, making it suitable for marking, incision, and dissection. Recently, an innovative water-jet integrated triangular tip knife (WJ) has been devised in order to improve procedural time with less instrument changes, as well as minimize adverse events. It comprises a thinner and more compact tip as well as jet function to allow saline injection after cutting without the need to switch devices (Figures 1 and 2). There have been several studies comparing the conventional triangular TT and WJ and suggesting that WJ can achieve similar clinical and procedural success rate, but with lower adverse effects, instrument changes, and intra-procedural coagulation devices[9].

Current literature lacks high-quality evidence to compare clinical outcomes of WJ and TT knives in POEM used for esophageal dysmotility disorders. The purpose of our systemic review and meta-analysis is to compare WJ and TT in terms of procedural and clinical success, and determine whether fewer adverse events and instrument changes could be achieved with the decreased procedural duration.

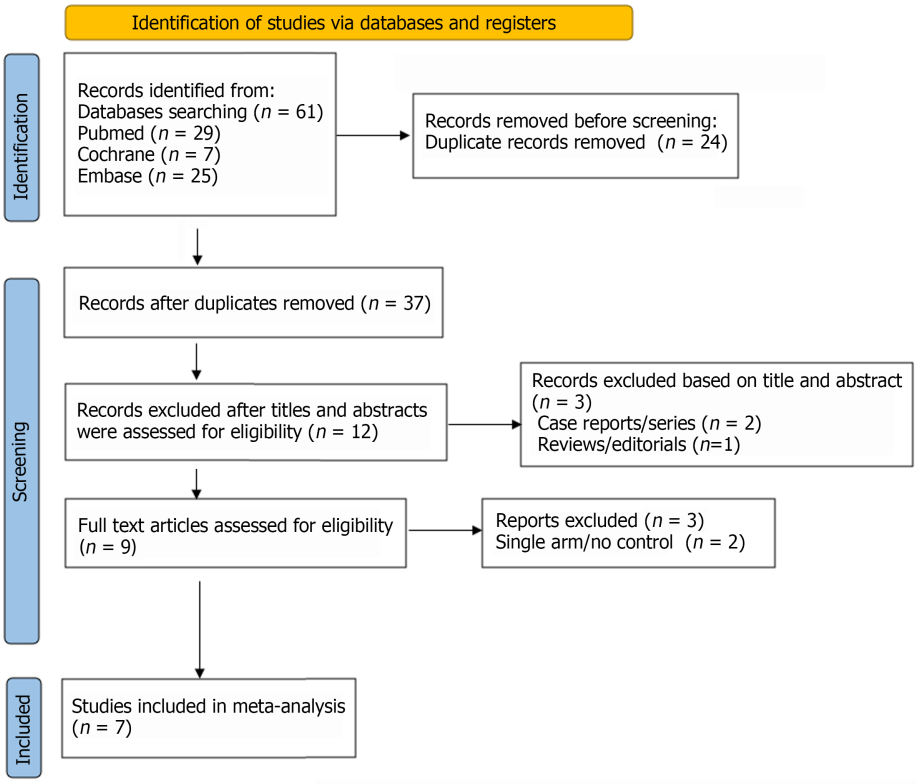

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Figure 1 Flow diagram with search results and selection criteria.

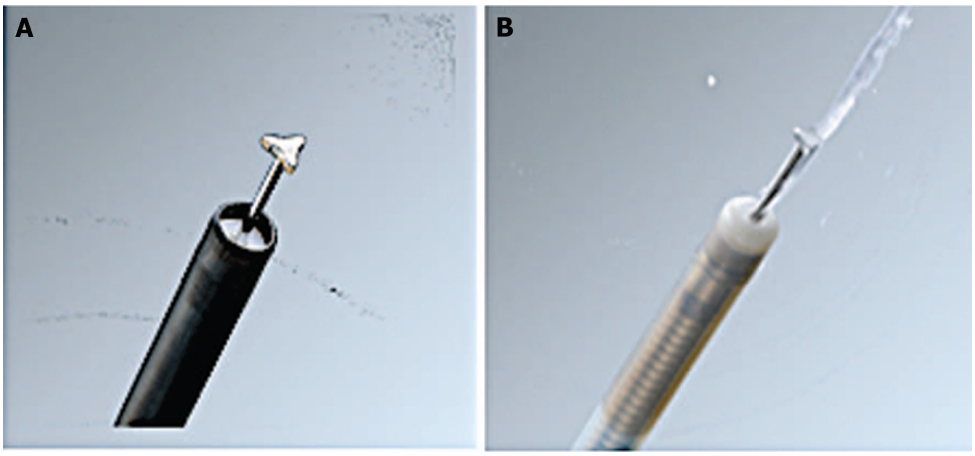

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Figure 2 It comprises a thinner and more compact tip as well as jet function to allow saline injection after cutting without the need to switch devices. A: Conventional triangular tip knife; B: Water-jet integrated triangular tip knife.

MATERIALS AND METHODS

Study selection criteria

Studies using triangular tip knife with integrated water jet as the instrument for peroral endoscopic myotomy were selected. Inclusion criteria included both adults and children with an indication of esophageal motility disorders for POEM treatment. Each study used POEM for achalasia, while 1 study did include other indications of diffuse esophageal spasm, nutcracker esophagus, and non-relaxing lower esophageal sphincter. Studies included patients that had been treated with prior therapies before POEM, of which majority were pneumatic balloon dilation.

Data collection, extraction, and quality assessment

Studies were systemically searched independently by two investigators (Belopolsky Y and Puli SR) in

Pubmed, Cochrane, and EMBASE. The search was performed from inception to May 2021. The search terms used were "peroral endoscopic myotomy" and "knife". Each abstract and title were screened for eligibility. All references at the end of each selected article were explored manually to retrieve additional studies. Any differences among investigators were resolved by mutual agreement. The interobserver variability was 1. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation methodology[10]. The agreement between reviewers for the collected data gave a Cohen κ value of 1.0.

Statistical analysis

This meta-analysis was performed by calculating weighted pooled effect *i.e.,* weighted pooled effect of patients with procedural success. First the individual study weighted pooled effect of procedural success was transformed into a quantity using Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion is calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the Mantel-Haenszel Method (fixed effects model) and DerSimonian-Laird Method (random effects model)[11,12]. Random effect model was used for meta-analysis in case of heterogeneity being statistically significant otherwise fixed effect models were applied. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots indicates the assigned weight to that study. In addition, odds ratio was used to represent dichotomous outcomes with a 95% confidence interval (CI), where a p value of <0.05 was considered statistically significant. The heterogeneity among studies was tested using I^2 and Cochran's Q test based upon inverse variance weights[13]. I^2 of 0% to 39% was considered as non-significant heterogeneity, 40% to 75% as moderate heterogeneity, and 76% to 100% as considerable heterogeneity. If P value is > 0.10, it rejects the null hypothesis that the studies are heterogeneous. The effect of publication and selection bias on the summary estimates was tested by both Harbord-Egger bias indicator and Begg-Mazumdar bias indicator[14]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[15,16].

RESULTS

Characteristics of studies

A total of 61 studies were retrieved by our search strategy. We reviewed these and excluded 52 studies based on titles and abstracts and reviewed full texts of remaining 9 studies. Finally, 7 studies met our inclusion and exclusion criteria[9,17-21]. This consisted of 2 randomised controlled trial (RCT) and 5 retrospective single center cohorts published between 2012 and 2021. Five studies were published full text articles while two studies were available as abstract poster presentations. Figure 1 shows the PRISMA flow chart to illustrate how final studies were selected. All pooled estimates were calculated using fixed and random effects models. The pooled effects estimated by both models were similar. All the pooled estimates given below are from the fixed effect model. Heterogeneity was assessed with *I*-squared, and publication bias with Egger's test.

A total of 558 patients were included in this meta-analysis. The mean age of patients' was 42.82 years (SD = 7.86) in the TT group and 37.03 years (SD = 12.29) in the WJ group, of which 59.57% were male in TT *vs* 52.51% in WJ group.

This review analyzed the various outcomes including procedural success, clinical successes defined as < 3 Eckardt score post-POEM, procedure duration, number of instrument exchanges, and usage of coagulation forceps. Most, but not all studies, included information on every variable that was analyzed. The studies that included information on the specific variable were included in the final analysis of that variable.

Clinical and technical success

Analysis showed weighted odds of technical success for POEM in TT group compared to WJ group to be 4.78 (95%CI = 0.22-102.47). In terms of clinical success, the standard accepted definition is a score of three or below in Eckardt score. The TT group had weighted odds of clinical success compared to WJ of 0.93 (95%CI = 0.29-2.97) (Figure 3). Publication bias calculated using Begg-Mazumdar gave Kendall's tau b value of -0.33 (P = 0.33). Heterogeneity calculated using I^2 was 0 indicating no significant heterogeneity among studies.

Procedural duration, number of instrument changes, and usage of coagulation forceps

Analysis of procedural duration for WJ had a weighted mean duration of 31.63 min (95%CI = 29.44-33.82) as compared to TT with weighted mean duration of 50.45 min (95%CI = 47.35-53.55). Regarding instrument changes, analysis showed a weighted number of instrument changes for TT of 11.92 times (95%CI = 11.15-12.70) *vs* WJ with weighted number of instrument changes of 2.21 times (95%CI = 1.98-2.45). The usage of coagulation forceps analysis showed for WJ the weighted usage of coagulation

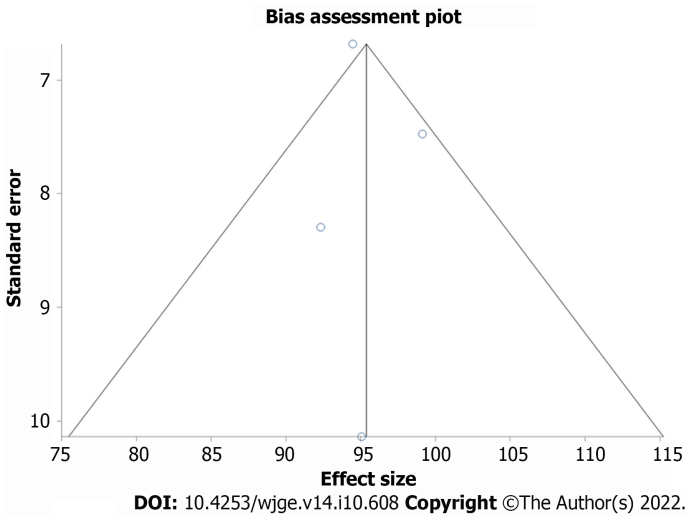

Figure 3 Funnel plot for publication bias of clinical success of triangular tip knife and water-jet integrated triangular tip knife.

forceps to be 2.63 times, (95%CI = 2.37-2.89) *vs* TT with weighted usage of coagulation forceps to be of 1.75 times (95%CI = 1.52-1.97).

Adverse events

The overall adverse events of TT compared to WJ had a pooled OR of 2.34 (95%CI = 1.34-4.23) (Figure 4). When evaluating the adverse event of subcutaneous emphysema, TT had a pooled OR of 1.46 (95%CI = 0.83-2.59) compared to WJ.

DISCUSSION

We performed a systemic review and meta-analysis of studies that compared conventionally used triangular tip knife and a knife using new integrated water-jet technology, in terms of several peri- and post-procedural outcomes. There was comparable procedural as well as clinical success, defined as post-operative Eckardt score of 3 or lower.

By pooling data across studies, our meta-analysis showed that WJ had statistically decreased procedural time of 32 min as compared to the TT of 50 min. For the endoscopist, that could theoretically increase procedural productivity. In addition, our analysis showed that both instrument exchanges and usage of coagulation forceps were decreased in the WJ group when compared to the TT group. Likely this can partially explain the shorter procedural duration, as well as indicate less intra-procedural bleeding with the less use of coagulation instruments.

The frequently reported adverse events of POEM include pneumomediastinum, mucosal perforations, pneumothorax, mucosal perforations, and subcutaneous emphysema[22]. In our meta-analysis, statistically adverse events were less likely to happen in the WJ group compared to the TT group. However, when examining one adverse event commented on in each study of subcutaneous emphysema, this was comparable among both groups as the confidence interval crossed one. Thus while overall adverse events were lower, it is difficult to discern which, if any, WJ could have lower risk of provoking.

Our study is the first in the literature to assess TT and WJ knives in POEM procedures for esophageal dysmotility disorders and analyze their effectiveness for the procedure. There are several strengths to our review. First, we included studies of WJ compared to standard TT technique, including 2 RCT. This allowed a more valuable comparison of procedural outcomes. Second, we conducted a systemic literature review with well-defined inclusion criteria, as well as careful exclusion of redundant studies with detailed extraction of data. Third, we separated studies that did not evaluate esophageal dysmotility disorders specifically, due to variable intra-procedural techniques that could have skewed the data.

While this study has included the most recent randomized controlled trials, these are few in our current available literature. Second, our conclusions apply to achalasia primarily, and did not include other indications for POEM other than those related to esophageal motility disorders. Finally, blinding of endoscopists was not possible and thus performance bias could have played a factor as well as inability to assess each performing endoscopist's skill level.

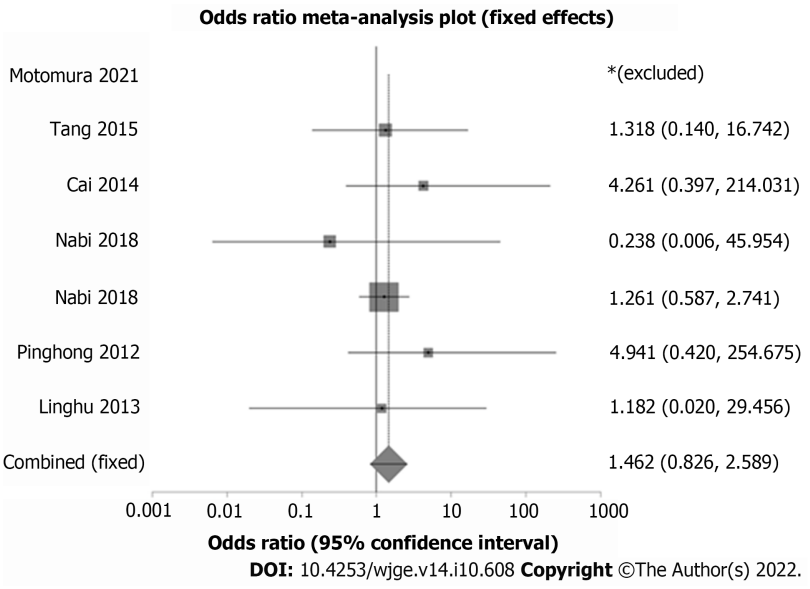

Figure 4 Forest Plot for assessing the odds ratio of adverse effects between usage of water-jet integrated triangular tip knife and triangular tip knife.

CONCLUSION

Water jet triangular tip knife has decreased procedural duration, number of instruments used, and usage of coagulation forceps over the conventional triangular tip knife. As such, this modality represents an attractive option for POEM. Our review represents the first review of the literature regarding water jet triangular tip knife in the management of esophageal dysmotility disorders using POEM. Collectively, the data supports using water jet triangular tip knife as a primary modality in terms of safety for the patient with less adverse events, with comparable technical and clinical success to the conventional triangular tip knife.

ARTICLE HIGHLIGHTS

Research background

This study is the first metanalysis to discover the differences between two main modalities for performing peroral endoscopic myotomy.

Research motivation

This study allows us to continue progressing in terms of instruments as it leads to continued success, but quicker and less adverse outcomes.

Research objectives

To compare two knives, conventional triangular tip as well as water jet integrated triangular tip knives.

Research methods

Clinical trials were examined and put together into metaanalysis.

Research results

This shows that water jet knife is comparable in terms of success to conventional traditional triangular knife with fewer adverse events and faster time.

Research conclusions

This study proposes new availability in instruments to the field of endoscopic myotomy.

Research perspectives

This allows future research to examine additional instruments and how to continue to further clinical success with better outcomes as well as ease for the endoscopist.

FOOTNOTES

Author contributions: Belopolsky Y and Puli SR contributed equally and substantially to the conception and design of the work, analysis, acquisition, interpretation of data for the work, and drafting the work and revising for important intellectual content; Belopolsky Y and Puli SR agree to be accountable for all aspects of work in ensuring questions related to accuracy and integrity of any part of the work are appropriately investigated and resolved; all authors wrote, read and approved the final manuscript.

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SYSTEMATIC REVIEWS

Laparoscopic Janeway gastrostomy as preferred enteral access in specific patient populations: A systematic review and case series

Max Murray-Ramcharan, Maria Camilla Fonseca Mora, Federico Gattorno, Javier Andrade

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Abstract

BACKGROUND

Nutrition is one of the fundamental needs of both patient and non-patient populations. General trends promote enteral feeding as a superior route, with the most common enteral access being the percutaneous endoscopic gastrostomy (PEG) as the first-line procedure, with surgical access including Witzel gastrostomy, Stamm Gastrostomy, Janeway gastrostomy (JG) as secondary means.

AIM

To describe cases and technique of laparoscopic Janeway gastrostomy (LJG) and perform a systematic review of the data.

METHODS

We successfully performed two LJG procedures, after which we conducted a literature review of all documented cases of LJG from 1991 to 2022. We surveyed these cases to show the efficacy of LJG and provide comparisons to other existing procedures with primary outcomes of operative time, complications, duration of gastrostomy use, and application settings. The data were then extracted and assessed on the basis of the *Reference Citation Analysis* (https://www.referencecitationanalysis.com/).

RESULTS

We presented two cases of LJG, detailing the simplicity and benefits of this technique. We subsequently identified 26 articles and 56 cases of LJG and extrapolated the data relating to our outcome measures. We could show the potential of LJG as a viable and preferred option in certain patient populations requiring

enteral access, drawing reference to its favorable outcome profile and low complication rate.

CONCLUSION

The LJG is a simple, reproducible procedure with a favorable complication profile. By its technical ease and benefits relating to the gastric tube formed, we propose this procedure as a viable, favorable enteral access in patients with the need for permanent or palliative gastrostomy, those with neurologic disease, agitation or at high risk of gastrostomy dislodgement, or where PEG may be infeasible.

Key Words: Laparoscopic Janeway gastrostomy; Janeway; Nutrition; Feeding tube; Enteral access; Reproducible

Core Tip: This systematic review identifies that the laparoscopic Janeway gastrostomy may be advantageous as a first line option for enteral access in specific patient populations, when compared to percutaneous endoscopic gastrostomy, or other surgical gastrostomy options, by virtue of the gastric tube created and its resistance to dislodgment and ensuing complications. Patients with high risk for tube dislodgment, including those with neurocognitive disorders, seizures, dementia, or patients requiring permanent enteral feeding access, may benefit the most from this intervention as a first-line option.

Citation: Murray-Ramcharan M, Fonseca Mora MC, Gattorno F, Andrade J. Laparoscopic Janeway gastrostomy as preferred enteral access in specific patient populations: A systematic review and case series. *World J Gastrointest Endosc* 2022; 14(10): 616-627

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INTRODUCTION

Nutrition is one of the fundamental needs of the hospitalized patient, with feeding access providing many unique challenges within different patient subgroups. From stable patients to those requiring intensive care unit treatment, all have specific metabolic demands and requirements necessary for progression towards optimization. Within a hospital setting, there have been extensive studies examining differences in outcomes between enteral feeds and parenteral routes, and many recent meta-analyses advocate for the use of enteric feeds either alone or supplemented by parenteral nutrition. Benefits identified include decreased incidence of respiratory infections, length of stay in the hospital [1], decreased morbidity and mortality, preservation of bowel function[2], and others. Nasogastric or nasoenteric tubes are typically the first-line forms of access in patients who require enteral feeds and are poorly suited for long term use due to discomfort from the tube, the unwillingness of conscious patients to endure placement, and other mechanical adverse features including frequent dislodgement or removal of tube and epistaxis from trauma during placement[3], and similar rates of aspiration events with both nasogastric and nasojejunal tubes[4]. Abnormal esophageal, pharyngeal or gastric anatomy may contribute to failure or difficulty of placement. Nasogastric or nasoenteric feeds are used for more short-term scenarios (less than 4 wk), whereas those requiring feeding for typically more than 6 wk may benefit from a gastrostomy[5].

For long-term feeding accesses, the percutaneous endoscopic gastrostomy (PEG) or percutaneous radiographic endoscopy (PRG)[6,7] remain the first line and preferred procedure. First described in the literature in 1980, the PEG has become widely popularized due to simplicity of performance, ability to perform as a bedside procedure, cost-effectiveness, and low complications profile by non-surgical approach[8]. What historically was the only viable option for feeding access, now the second line in the event of failure or infeasibility of PEG, exists the surgical gastrostomies (and jejunostomies). The Stamm gastrostomy, introduced in 1894[9]; is achieved *via* an incision made in the anterior stomach wall with a purse-string suture securing a tube brought out through the anterior abdominal wall. Performed open or laparoscopically, this technique is simple to perform with low morbidity and revision rates[10]. The Witzel gastrostomy, initially described in 1891, is performed with a tube or catheter (exiting the anterior abdominal wall) introduced into a gastrostomy on the anterior stomach, with parallel folds fashioned into a tunnel around the tube. This procedure had limited response as a gastrostomy, and multiple variations have led it to be performed instead as a jejunostomy creation technique. As a result, this is a rarely performed gastrostomy procedure with minimal literature documenting its utility as such[9]. The Janeway gastrostomy, the focus of this paper, was introduced into practice in 1913, with the unique

creation of a gastric tube from the anterior stomach wall exteriorized as a stoma boasts the advantage of permanence and resilience in the setting of tube dislodgement in comparison with other techniques[9]. Initially used for feeding in cases of advanced head and neck tumors[11], following several modifications, this technique is commonly performed laparoscopically for a variety of indications. This literature review explores the versatility of the laparoscopic Janeway gastrostomy (LJG) for patients requiring long-term or permanent enteral feeding access with the aid of two presented cases.

MATERIALS AND METHODS

We retrieved the records of the patients who underwent LJG creation on (n = 2) in Woodhull Hospital Center of New York Health and Hospitals (Brooklyn, New York) from 2021 to 2022. Two patients were identified and their respective clinical courses relevant to their procedure were documented, making note of technical details, ensuing postoperative courses and complications.

Search strategy for systematic review

A comprehensive search of the literature was conducted through MEDLINE/PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews to identify relevant articles. Before initiation of the search authors determined titles, keywords, and text words of importance to apply in the search. The database search included a combination of the following keywords: Janeway and gastrostomy. Cross-referencing was then performed to identify additional relevant articles. A data collection form was used to extract pertinent information including inte-rvention, treatment, and various outcome measures.

Study selection and characterization of articles

Relevant studies were identified and selected by individual reviewers separately based on title and abstract content. Supporting evidence included randomized and non-randomized controlled trials, systematic reviews, prospective and retrospective studies, case series, reviews, and letters to editors. Analysis and evaluation of Spanish articles were performed independently by native Spanish-speaking physicians.

Inclusion and exclusion criteria

The articles included in this selection were English or Spanish articles published between 1984 and 2022. We included patients of all ages and articles of all types. Exclusion criteria consisted only of articles written in other languages such as French or German, to prevent inaccurate translation. This search was performed and reviewed for inclusion in the review by authors MMR and MCF independently on 22nd February 2022.

Quality assessment

The methodological quality of the studies was assessed using the 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practices Guidelines: Evidence Rating (Table 1). Data quality and recommendations for clinical application were categorized based on the evidence level.

RESULTS

Systematic review

An initial assessment of articles' abstracts and titles was performed with a total preliminary outcome of 26 articles. After this initial screening, the 26 articles were evaluated in more detail with proper screening against inclusion and exclusion criteria. 15 articles were excluded; of those three had content in German and two in the French language, the remaining twelve referred to content that was not pertinent to the outcomes being evaluated in this review, by either discussing animal trials or JG for additional procedures (trans-gastric endoscopic retrograde cholangiopancreatography in complicated anatomy) rather than enteral access. An addition of five references was found and of those, three were included after cross-referencing articles. After a thorough selection of articles using the PRISMA criteria (Figure 1) a total of 11 articles resulted in the following breakdown: Five case series, one case report, two short communications articles with associated case reports, one technical innovation article with associated case series, one comprehensive review article, and one original article.

Results from a systematic review

From the analyzed studies on LJG (Table 2), of the total 56 patients with LJG 43 patients had documented their operative times, of which the total average was 37.66 min (40 min by Ritz *et al*[12], 35 min

Table 1 2010 American association of clinical endocrinologists protocol for production of clinical practices guidelines - evidence rating

Numerical descriptor (evidence level)	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials
1	Randomized controlled trial
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study/Retrospective cohort study
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study)
3	Consecutive case series
3	Single case reports
4	No evidence (theory, opinion, consensus, or review)

1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; 4 = no evidence. CCS: Consecutive case series; CSS: Cross-sectional study; MRCT: Meta-analysis of randomized controlled trials; MNRCT: Meta-analysis of nonrandomized prospective or case-controlled trials; NRCT: Nonrandomized controlled trial; NE: No evidence; PCS: Prospective cohort study; RCCS: Retrospective case-control study; RCS: Retrospective cohort study; RCT: Randomized controlled trial; SS: Surveillance study; SCR: Single case reports.

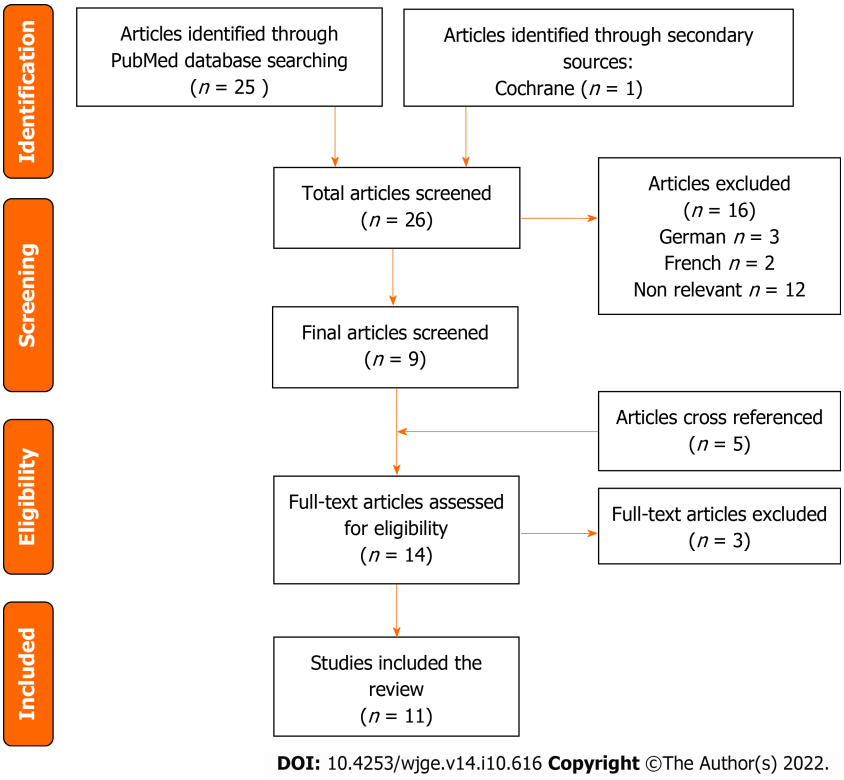

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Figure 1 PRISMA flow chart for articles and studies selection.

by Serrano *et al*[13], and 38 min by Raakow *et al*[14]). Mean usage times (MUTs) were documented in 36 patients and 3 articles. We noted 13 total complications and 0 mortalities related to the procedure. For the 102 patients that underwent open Janeway gastrostomies (OJG) (Table 3); twelve patients had documented MUTs, however none of them had anticipated future removal at the time of documented follow-up. Of this the average follow-up was 7.5 mo (9 mo reported by Koivusalo *et al*[15], and six months by Abdel-Lah *et al*[16] The remaining authors did not consider this as an endpoint.

Table 2 Literature reported cases of laparoscopic Janeway gastrostomies

Ref.	Evidence rating	Case	Outcomes	Complications
Haggie *et al*[18], 1992	3	*n* = 1 pt; Age= 65 yr (M); Esophageal occlusion of pharyngeal SCC s/p CTX and RTX	ORT: N/M; MUTs: 3 wk (death 2/2 primary disease)	Leakage of gastric contents easily managed; D: 1; R: 1; TC: 2
Serrano *et al*[13], 1994	3	*n* = 7 pt; Age = 48-83 yr; Esophageal cancer stage IV: 85% (*n* = 6); Traumatic peri-esophageal hematoma: 14.2% (*n* = 1)	ORT: 30-40 min. Average 35 min. MUTs: N/M	TC: 0; D: 0; R: 0; Mortality: 0
Ritz *et al* [12], 1998	3	*n* = 15 pt; Age average: 61 yr; Esophageal or paraesophageal tumors	ORT: 20-55 min. MUTs: 3.5 mo (death)	Stoma necrosis to Witzel gastrostoma: 6.6% (*n* = 1); Self-limiting skin irritation: 20% (*n* = 3); D: 0; R: 0; TC: 2
Molloy M *et al*[17], 1997	3	*n* = 2 pt (M); Age= 63 yr and 77 yr; Organic neurologic disorders + pulled out PEG (placed 48 h prior); Perforation along greater curvature (minimal contamination)	ORT: N/M. MUTs: N/M	C: N/M; D: N/M; R: N/M
Raakow *et al*[14], 2001	2	*n* = 21 pt (19 M; 2 F); Age = 53-78 yr; Extensive tumors of: Hypopharynx 57.1% (*n* = 12) Esophagus 42.8% (*n* = 9); Prior UGI surgery 19% (*n* = 4) to (2 OCh, 1 PCJ, 1 repair DP)	ORT: 24-50 min. Average 38 mins. MUT: 3.4 mo 2/2 death due to primary	C: Self-limiting skin irritation (method dependent): 9.6% (*n* = 2); D: N/M; R: N/M; Mortality from advanced cancer; MUTs: 26 d to 6.5 mo (average 3.4 mo)
Tous Romero *et al*[19], 2012	2	*n* = 57 pt; Age = 51 yr; 10 LJG, 47 OJG; Esophageal cancer: 38.6% (*n* = 22); Head & neck: 26.3% (*n* = 15); Neuro deficit 26.3% (*n* = 15)	ORT: N/M. MUTs: N/M	TC: 5 (some patients had multiple complications); D: N/M; R: N/M; Gastric content leakage: 30% (*n* = 3); Abd wall irritation: 30% (*n* = 3); No C: 50% (*n* = 5); Exudate: 10% (*n* = 1); Exudate with + culture: 20% (*n* = 2); Granuloma: 10%(*n* = 1); Balloon rupture: 10% (*n* = 1); Loss of peristomal content: 0

C: Complications; CXT: Chemotherapy; D: Dislodgement; DPr: Duodenal perforation; F: Female; M: Male; GT: Gastric tube; LJG: Laparoscopic Janeway gastrostomy; JT: Jejunostomy tubes; LE: Life expectancy; MUTs: Mean usage times; n: Number of patients; N/M: Not mentioned; OCh: Open cholecystectomy; ORT: Operating time; Pt: Patients; PCJ: Pancreatic cyst jejunostomy; R: Replacement; RXT: Radiotherapy; SG: Stamm gastrostomy; SCC: Squamous cell carcinoma; UGI: Upper gastrointestinal.

Laparoscopic Janeway gastrostomy technique

There exist several modifications of the original JG, with further modifications introduced with the inception of laparoscopy into commonplace surgical practice[14]. We describe the laparoscopic technique used in the ensuing case presentations. The patient was placed supine with a slight reverse Trendelenburg to better visualize the stomach. Port sites were placed as follows, a 12 mm supraumbilical port, a 5 mm port to the right of the umbilicus and a 12 mm in the left upper quadrant. The anterior surface of the stomach along the greater curvature was retracted towards the anterior abdominal wall (Figure 2A), and an EndoGIA stapler 45 mm purple cartridge was used *via* the right 12 mm port to create a gastric tube approximately 5 cm - 6 cm in length, 1cm wide, by described Janeway technique (Figure 2B). The gastric tube was brought out of the abdomen *via* the leftmost port. A Carter-Thomason trans-fascial port closure device was used to place 3 sutures circumferentially around the base of the gastric tube, anchoring it to the anterior abdominal wall (Figure 2C). Pneumoperitoneum was discontinued to evaluate the resting anatomic position of gastrostomy. The now externalized tip of the gastric tube was then opened and matured to the skin in standard fashion. The matured gastrostomy was then cannulated with a 24 Fr Gastrostomy tube. Pneumoperitoneum was re-established under low pressure and gastrostomy and staple line inspected, demonstrated gastrostomy tube in a good position with the intragastric balloon inflated, and no evidence of immediate complications. The operation was completed with discontinuation of pneumoperitoneum and removal of trocars with appropriate port site closure.

Cases series

Patient A: This is a 77-year-old woman with a past medical history of dementia, hypertension, and depression who was being managed in the hospital for altered mental status and mental decline following infection with coronavirus disease 2019 (COVID-19) a few months prior (Table 4). During the hospital stay, the patient experienced a further decline from baseline, with worsening dementia and refusal of oral intake and malnutrition. The primary team requested enteral feeding access, and with the agreement of the patient's healthcare proxy, we advocated for LJG tube placement. We suggested this procedure due to the patient's dementia, need for permanent/long-term feeding, and a high risk of the patient pulling out tubes. The procedure was performed by the technique described above, and the patient was followed postoperatively. There were no noted complications, and the gastrostomy tube

Table 3 Literature reported cases of open gastrostomies

Ref.	Evidence rating	Case	Outcomes	Complications
McGovern *et al* [21], 1984	3	*n* = 14 children (> 7lb); Severe cerebral palsy without pharyngeal musculature coordination and risk of aspiration	ORT: N/M, MUTs: N/M	C: GT stenosis treated with dilation: 7.14% (*n* = 1); Stomal granulations treated with cautery: 7.14% (*n* = 1); Mortality: 0; D: N/M; R: N/M
Laughlin *et al* [20], 1989	3	*n* = 5 pt. Advanced esophageal cancer; Age/gender: N/M	ORT/MUTs: N/M	C: Stomal tip necrosis with stomal stenosis: 20% (*n* = 1); Mortality: 0; D: N/M; R: N/M
Vassilopoulos *et al*[11], 1998	3	*n* = 24 pt (21M; 3F); Age average: 67.19 yr; Advanced head/neck cancer; Advanced UGI malignancy: 1.2% (*n* = 5); Prior UGI surgery: 0.48% (*n* = 2)	ORT: < 40 min; MUTs: N/M	C: Midline wound SSI treated with antibiotics: 16.6% (*n* = 4); Mortality: 0; D: N/M; R: N/M
Koivusalo *et al* [15], 2006	33	*n* = 4 pt; Age = 0-6 yr; Recurrent gastrostomy prolapses and peristomal infection undergoing modified OJG revision; 3: OSG to 2 closure + PEG; 1: Initial PEG; Prior abdominal surgeries (OGT/PEG)	MUTs: 9 mo	C: 0;D: N/M; R: N/M content
Abdel-Lah *et al* [16], 2006	3	Total procedure 287: JT: 46% (*n* = 167); SG: 18% (*n* = 40); OJG: 4% (*n* = 8); SNY double lumen: 32% (*n* = 72); Head & neck cancer; Total permanent gastrostomies *n* = 27: Balloon catheter/Fontan (LE < 37 d): *n* = 19; OJG (LE > 6 mo): *n* = 8	MUTs; JG = 164 d	Morbidity 12.5% (*n* = 5): D (Migration)/peristomal abrasion- no fixation to parietal peritoneum; Mortality (open jejunostomy) 4.2% (*n* = 12); Esophageal 3% (*n* = 9); Esophagojejunal: 1.2% (*n* = 3); R: N/M
Tous Romero *et al* [19], 2012	2	*n* = 57 pt; Age average: 57, 51 yr 10 LJG, 47 OJG; Esophageal cancer: 38.6% (*n* = 22); Head & neck: 26.3% *n* = 15); Neuro deficit: 26.3% (*n* = 15)	ORT/MUTs: N/M	Gastric content leakage: 89.4% (*n* = 42); Abd wall irritation: 83% (*n* = 39); No C: 2.1% (*n* = 1); Exudate: 23.4% (*n* = 11); Granuloma: 4.3% (*n* = 4); Balloon rupture: 21.3% (*n* = 10); Loss of peristomal content: 17% (*n* = 8)

C: Complications; CXT: Chemotherapy; D: Dislodgement; DPr: Duodenal perforation; F: Female; M=Male; GT: Gastric tube; GC: Great curvature; LJG: Laparoscopic Janeway gastrostomy; JT: Jejunostomy tubes; LE: Life expectancy; MUTs: Mean usage times; *n*: Number of patients; N/M: Not mentioned; OCh: Open cholecystectomy; OJG: Open Janeway gastrostomy; ORT: Operating time; Pt: Patients; OSG: Open stamm gastrostomy; PCJ: Pancreatic cyst jejunostomy; R: Replacement; RXT: Radiotherapy; SG: Stamm gastrostomy; SCC: Squamous cell carcinoma; SSI: Surgical site infection; UGI: Upper gastrointestinal.

Table 4 Our case series of post coronavirus disease 2019 era

Case	Selection of LJG *vs* others	Indications	Outcomes	Complications
Patient A: 77 yr female	Instead of PEG; Patient is high risk of pulling out tubes	Worsening dementia and AMS. Need for long term/permanent feeding	ORT: 87 min. MUTs: 3 mo	D: 0; R: 0; TC: 0
Patient B: 58 yr male; s/p tracheostomy and recent PEG tube placement	Instead of PEG. C: Dislodgement of PEG and septic shock	Cerebral palsy, seizure disorder self-removed PEG. Prior PEG removal + replacement	ORT: 76 min. MUTs: 3 mo	D: 0; R: 0; TC: 0

LJG: Laparoscopic Janeway gastrostomy; PEG: Percutaneous endoscopic gastrostomy; D: Dislodgement; R: Replacement; C: Complications; N/M: Not mentioned; MUTs: Mean usage times; ORT: Operating time.

was used for feeding immediately postoperatively without any complications noted and was discharged safely the following day. The gastrostomy tube remained intact with no complications until the patient passed away as a result of complications of primary disease while in hospice care 3 mo later.

Patient B: This is a 58-year-old man who resides in a nursing home, with a past medical history of cerebral palsy, seizure disorder, diabetes, hypertension, and a past surgical history of tracheostomy and recent PEG tube placement after distant COVID-19 pneumonia (Table 4). After the PEG was placed, the patient was discharged back to his nursing home once his pneumonia resolved, during which time he removed his PEG tube in instances of agitation multiple times, each with subsequent replacement. Several months after initial placement, the patient was brought to the emergency department in septic shock with a tender and distended abdomen. Due to his neurologic conditions, he was unable to provide any history, and he underwent a computed tomography scan which revealed that the balloon of his gastrostomy feeding tube was embedded in the anterior abdominal wall, and there was significant subcutaneous air and fluid along the rectus sheath adjacent to the gastrostomy tube along with a fragment of the apparatus within the stomach. (Figure 3A and B). He underwent an emergent surgery where tube feeds and purulent fluid were found within the soft tissue above the fascia and the

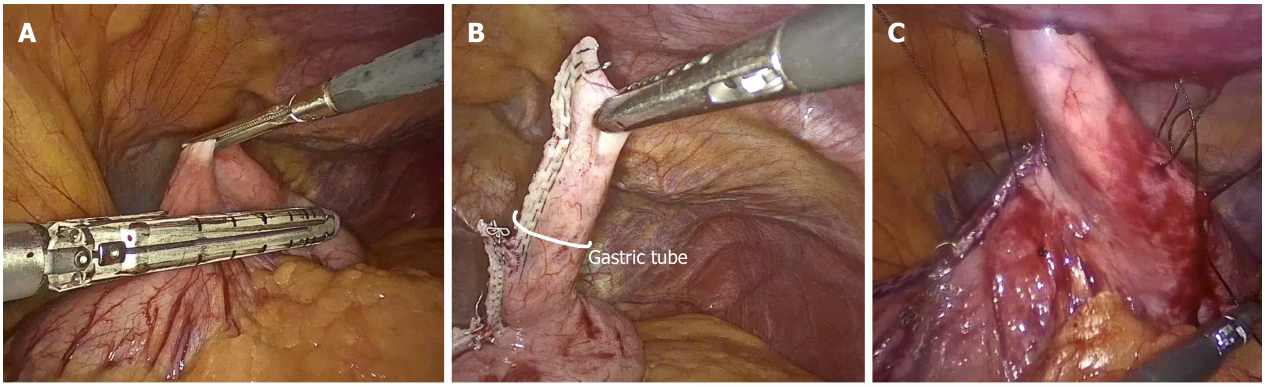

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Figure 2 The anterior abdominal wall of laparoscopic Janeway gastrostomy technique. A: Positioning of stapler for gastric tube creation along greater curvature; B: Gastric tube demonstration; C: Gastric tube being externalized and placement of anchoring sutures.

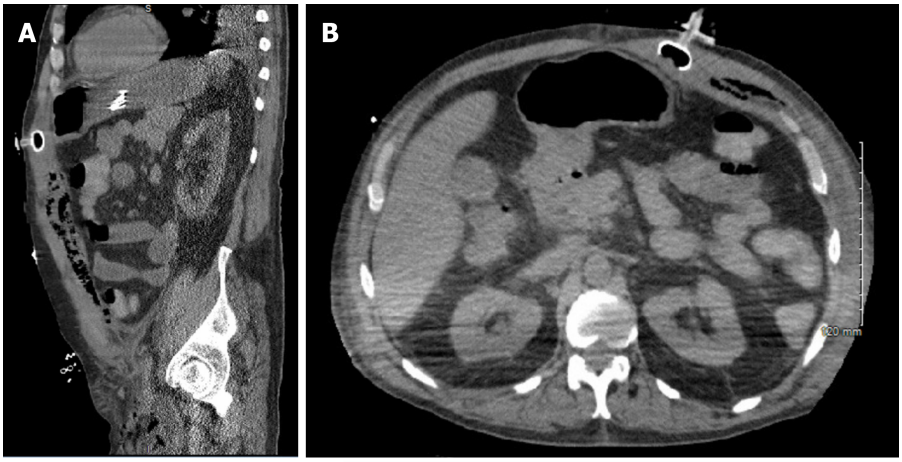

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Figure 3 Computer tomography images related to case B. A: The sagittal view; B: The Axial view.

abdominal cavity. He underwent debridement and washout of this fluid, fascia closed and the wound was left to heal by secondary intention. After he recovered from septic shock in the intensive care unit, a skin graft was performed due to poor healing from this procedure (Figure 4A and B). Due to his hostile anatomy after these procedures, his high risk of removal or dislodgement of the tube, and the continued need for permanent feeding access due to his cerebral palsy, we elected to perform LJG. The procedure was by the technique described above, and the patient was followed postoperatively. There were no noted complications, and the gastrostomy tube was used for feeding immediately postoperatively. The gastrostomy tube was removed by the patient twice within the first 3 wk postoperatively (postoperative days 11 and 18), and two more times within the first 2 mo post-procedure (postoperative days 48 and 61) with subsequent replacement without issue. The patient was discharged approximately 2 mo after the procedure after the management of his primary disease, during which time no further complications were noted. A month later, the patient passed away as a result of complications of primary disease while in hospice care.

DISCUSSION

When comparing the standard of care (PEG) to LJG, we can see advantages concerning the fistula tract. In a PEG, there is rapid obliteration of the fistula if the tube becomes dislodged, which allows for only a small window in which replacement of the tube may be possible. In these settings, repeat instrumentation or another procedure for enteral access may be required[17], in addition to possible complications of the gastric leak[18]. The LJG does not share this complication, due to the mucous layer surrounding the gastrostomy tube, as well as the maturation of the gastric tube to the skin. A feeding tube can be safely replaced without concern, or in certain circumstances may be removed and replaced

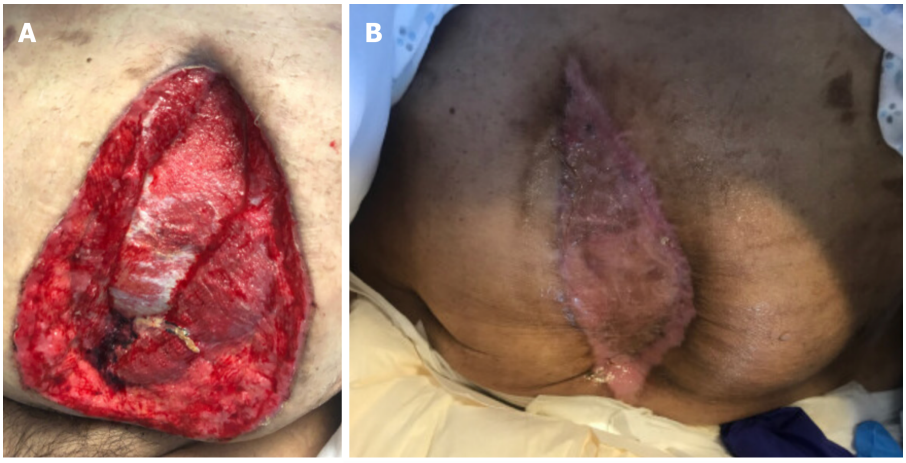

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Figure 4 Patient B's skin graft. A: Anterior abdominal wall view before skin grafting; B: Anterior abdominal wall view after skin grafting and appropriate healing, to illustrate abdominal wall anatomy.

freely and intermittently when feeding is needed. Additionally, this type of gastrostomy is performed *via* an objectively easy and reproducible procedure with few steps. We draw reference to the described cases above, both performed almost entirely by surgical residents and in an identical fashion. Even in the case of patient A, with prior intra-abdominal surgery as well as abdominal wall surgery, the procedure was performed with no significant adjustments. Several modifications to the original technique exist; in our cases we utilized trans-fascial anchoring sutures to the base of the gastric tube. This serves to relieve any tension on the gastric tube, increasing the surface area of anterior abdominal wall adherence. Another modification is the use of a port site as the site of the gastrostomy, limiting additional incisions. In earlier techniques of LJG, the gastric tube was created with the base of the gastric tube near the lesser curvature, in contrast to the modification used in the presented case where the base was at the greater curvature (Figure 3). This simple but strategic modification described in our cases allows for preservation of the blood supply of the gastric tube by the gastro-epiploic vessels, as well as allows for more desirable positioning of the gastrostomy lateral to the midline with an exit through the rectus muscles. The fixation of the exteriorized gastrostomy to the skin, akin to the maturation of an ostomy, is not performed in surgical gastrostomies. This creates a definitive track that leads to the permanence and longevity of the LJG. The gastrostomy creation not only spares the need for a constant indwelling catheter but also provides continence as it exits through the rectus abdominis[12], with a sphincteric mechanism *via* the rectus muscles preventing reflux or incontinence[14]. This configuration may be advantageous in the population of patients with disorders such as seizures or cerebral palsy. Compared to PEG which lacks an anti-reflux mechanism, the sphincter created during the LJG may be more preventative against complications of convulsive patterns including reflux, leakage from the stoma, and stomal prolapse[15].

This systematic review was performed with a focus on technical ease and reproducibility of procedure, resistance to complications such as tube dislodgement, and evaluating the use of the LJG as a permanent or long-term feeding access option as it compares to the alternatives. In terms of operative times, most of the studies published share a very similar range and mean duration; with an average time of 35.3 min for all the 43 patients with their times documented. We propose three main reasons for the difference between these studies and the 2 case reports of our own (with an average operating time of 81 min). One is likely due to the procedures in our studies being performed almost entirely by residents, with a large focus on education and laparoscopic skill development. The other proposed reason is that in "Patient B", the procedure was initially delayed by a transient intolerance to pneumoperitoneum, after which, following optimization by anesthesia, we were able to proceed. This delay was factoring into the total operative time which is a series of only 2 patients may lead to a greatly extended average operating time. The third proposed reason for time discrepancies relates to the technique used; in our two described cases, we employed the use of intracorporeal anchoring sutures to affix the base of the gastric tube to the anterior abdominal wall - an optional modification to the LJG to provide additional support, not performed in other reports. With regards to use as a long-term option for feeding access, there exists an objective theoretical advantage for LJG. By the creation of a gastric tube and maturation to the skin, a technique unique to the JG/LJG, there cannot be spontaneous closure of the fistula, making this ideal for long-term, palliative, or permanent enteral access. This systematic review looked at the documented MUTs of LJG (Table 2) to establish its role in longevity. This proved difficult, since the LJG by these benefits, was used quite extensively in populations consisting of terminal patients, or patients residing in nursing homes with expectedly poor follow-up.

We acknowledge that the goals of this paper are to demonstrate characteristics of the laparoscopic Janeway specifically, but we believe that with regards to MUT post-procedure, we may be able to utilize data from the subset of OJG analyzed (Table 3), as the result of these procedures is the same regarding gastrostomy use. The average MUT between the LJG and OJG groups is approximately 4 mo, however these results obtained do not reflect the true permanence of this procedure. In the above studies we had no documented cases of reversal of the gastrostomy, and due to the essential nature of the indications for this procedure, we can extrapolate that the LJG likely lasted the intended length of time: the rest of the respective patients' lives. Of the 56 patients who underwent LJG in the analyzed articles, we note 13 total complications and 0 mortalities related to the procedure; reported mortalities were related to the medical condition itself as seen in our case series. We attempted to stratify these into major and minor complications. The only identified major complication occurred in 1 patient in this series, in the case of Ritz *et al*[12], which documents a case of stomal necrosis, attributed by the authors to the creation of a gastric tube that was too small. This case necessitated surgical revision and conversion to a Witzel gastrostomy, with the remainder of the post-operative course unremarkable. With regards to the minor complications, we note 8 total cases of skin irritation[12,14,19] all of which were self-limiting. Tous Romero *et al*[19] documented one case in which a stoma granuloma formed, and this did not affect the functioning of the gastrostomy nor the quality of patient life, demonstrating the preferable complication profile for the LJG.

A significant complication of most gastrostomy procedures is tube dislodgement. This highlights possibly the most desirable feature of the LJG, that tube dislodgement at any time post-operatively does not cause any complication and poses no significant risks to the patient. This benefit is not only theoretical; we see it in clinical practice. In Raakow *et al*[14], the authors had the gastrostomy tubes removed from the gastrostomy intermittently, beginning on postoperative days 10-14 without any complications related to removal or reinsertion. We saw this in our case of "Patient B" in the presented clinical case, where the patient himself removed the gastrostomy tube on postoperative days 11, 18, 48, and 61, with no concerning sequelae following bedside replacement. There may have been a need for reoperation, especially with the first two removals, had the procedure been any other gastrostomy than an LJG. Comparing the complication profile of the LJG to that of a PEG, Ritz *et al*[12] demonstrate that PEG has a complication rate up to 30% (minor) and 9% (major) with a 1%-2% mortality. This is further corroborated by Rahnemai-Azar *et al*[6] in a comprehensive literature review, which identifies 8 minor and 6 major complications associated with PEG. The dislodgement of the PEG tube is seen to occur in approximately 12.8% of patients, with management strategies including replacement or new PEG or surgical gastrostomy creation. Other major complications of PEG described that may be mitigated by the use of LJG include buried bumper syndrome, not using the classic PEG tube, and hollow viscus inadvertent injury, as direct visualization is possible[6].

Comparing LJG to other surgical gastrostomies, data from the existing literature advocates a more benign complication profile as compared to the other surgical alternatives. Ritz *et al*[12] compared complications of open Witzel, Stamm, Kader, and Janeway gastrostomy. The OJG had a complication rate of 0%-25%, with a mortality rate of 0%-11%, favorable to that of the other open surgical alternatives with a collective complication rate of 13%-42% and a mortality rate of 10%-23%. These rates in OJG were then compared to those of LJG, with LJG having a 0%-6% complication rate and 0% mortality[20,21]. For completion, laparoscopic Kader gastrostomy was also compared to the rates for LJG, with complication rates of 6%-9% and mortality rate of 0%-5%, illustrating the preferable results of the LJG. Raakow *et al*[14] further supplemented these results by noting that when the Janeway technique is applied, the risks of developing postoperative leakage are notably decreased (approximate 0%-1%) when compared to approximately 9% as seen in the other surgical gastrostomies[14]. Abdel-Lah *et al*[16] in a more recent study, compared the LJG directly to the OJG. However, no statistical differences were noted given the variety of the population and the lack of specific primary outcomes. This highlights the need for more studies to investigate these differences.

LIMITATIONS

We identify several limitations in this literature review. Firstly, the majority of the studies analyzed had a relatively low sample size, with a total of 158 patients analyzed (56 patients with LJG and 102 with OJG). Another limitation is that there are no randomized controlled trials available in the literature that compares LJG to other gastrostomy creation techniques. This is the gold standard for inferring causation from correlation, and without this type of study we acknowledge less strength of the presented literature. In addition, there is limited research on the use of LJG, as evidenced by the small number of articles retrieved with broad search terms. Another limitation of this review is that many of the indications for LJG described in the literature are for palliative purposes with a large cohort of patients having advanced-stage cancers. This confounds the investigated MUT of the gastrostomy tube, which may have been longer had the patients not had poor prognoses. This limits the ability of this study for long-term analysis. Lastly, we noted that scarce recent data has been published on JGs, as evidenced by including articles published over 20 - 40 years ago. A proposed reason for this chronology is that

surgical gastrostomies have been seldom performed in recent years due to the popularity of the PEG and indicates strong potential for future studies where recent data is lacking.

CONCLUSION

The LJG is a viable technique for the creation of permanent or long-term enteral access, by its simple, reproducible technique and desirable complication profile, especially with for tube removal or dislodgement. As seen in many of the cases reviewed, this can be performed by advanced laparoscopists, surgical residents, and general surgeons without formal laparoscopic fellowship training. We acknowledge the data supporting PEG as a first-line feeding option, and advocate that the LJG should be strongly considered as a first-line option in specific patient populations, those who require permanent enteral access who may be at risk of tube dislodgement or removal due to agitation or neurologic disease. Another role for LJG as a first-line option may be in the setting where PEG is infeasible, for example, in cases of advanced head and neck cancer, severe abdominal wall scarring, and inability to get transillumination, as seen in the cases reviewed. LJG also has a beneficial potential role as a second-line option should a PEG be unable to be performed or unsuccessful, for any sign of long-term feeding access. This literature review, besides describing the many advantages of this procedure, has made us aware of the need for further study and randomized controlled trials of this promising technique.

ARTICLE HIGHLIGHTS

Research background

LJG, when initially described, was used as one of the first-line enteral access options, and has since been replaced by the advent and popularity of PEG. The significance of this study is that it demonstrates that the laparoscopic modification may be an acceptable first-line procedure for specific indications due to its longevity and ease of completion.

Research motivation

The main topics of this paper are that LJG may have more clinical relevance than previously considered. The problems this paper addresses is the complication rate including those caused due to dislodgement and tube removal with the PEG procedure. This procedure ameliorates these complications and may have a role in first-line access for specific indications.

Research objectives

The main objectives of this project was to describe cases of LJG as well as perform a systematic review of the available data as it relates to LJG for enteral access. We realized from this review, that LJG may serve as a viable alternative to PEG as a first-line option for enteral access in specific populations. The significance of this realization can result in lower morbidity and mortality as it relates to the complications of PEG dislodgements in specific patient populations.

Research methods

A systematic review was performed of all available data of LJG relating to use for enteral access. This data was analyzed by the reviewers to realize the objectives. To our knowledge, no large systematic reviews of LJG have been recently performed for this purpose.

Research results

Our findings describe relatively low rate of complications from LJG, largely as a result of the permanent gastrostomy tube formed in the procedure. We also note significant technical ease in completion of the procedure.

Research conclusions

This study proposes that LJG may be a viable alternative to PEG as a first-line procedure in specific patient populations.

This study describes the laparoscopic modification of Janeway gastrostomy and notes the technical ease and reproducibility.

Research perspectives

The direction for future research in this topic may include prospective studies and randomized controlled trials to determine true comparative data between LJG and PEG and other gastrostomy alternatives, and also to provide objective data to guide optimal patient selection.

FOOTNOTES

Author contributions: Murray-Ramcharan M conceptualized research study and both Murray-Ramcharan M and Fonseca Mora M designed the research study; Murray-Ramcharan M and Fonseca Mora M performed the research; Gattorno F and Andrade J contributed analytic tools and editing; Murray-Ramcharan M and Fonseca Mora M analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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CASE REPORT

Tracheoesophageal fistulas in coronavirus disease 2019 pandemic: A case report

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Abstract

BACKGROUND

Tracheoesophageal fistulas (TEFs) can be described as a pathological communication between the trachea and the esophagus. According to their origin, they may be classified as benign or malignant. Benign TEFs occur mostly as a consequence of prolonged mechanical ventilation, particularly among patients exposed to endotracheal cuff overinflation. During the severe acute respiratory syndrome coronavirus 2 virus pandemic, the amount of patients requiring prolonged ventilation rose, which in turn increased the incidence of TEFs.

CASE SUMMARY

We report the cases of 14 patients with different comorbidities such as being overweight, or having been diagnosed with diabetes mellitus or systemic hypertension. The most common symptoms on arrival were dyspnea and cough. In all cases, the diagnosis of TEFs was made through upper endoscopy. Depending on the location and size of each fistula, either endoscopic or surgical treatment was provided. Eight patients were treated endoscopically. Successful closure of the defect was achieved through over the scope clips in two patients, while three of them required endoscopic metal stenting. A hemoclip was used to successfully treat one patient, and it was used temporarily for another patient pended surgery. Surgical treatment was performed in patients with failed endoscopic management, leading to successful defect correction. Two patients died before receiving corrective treatment and four died later on in their clinical course due to infectious complications.

CONCLUSION

The incidence of TEFs increased during the coronavirus disease 2019 pandemic (from 0.5% to 1.5%). We believe that endoscopic treatment should be considered as an option for this group of patients, since evidence reported in the literature is still a growing area. Therefore, we propose an algorithm to lead intervention in

patients presenting with TEFs due to prolonged intubation.

Key Words: Tracheoesophageal fistula; COVID-19; Endoscopy therapy; Gastroenterology therapy; Case report

Core Tip: Due to the significant increase of tracheoesophageal fistulas in the context of severe coronavirus disease 2019 (COVID-19) pneumonia, and the high frequency of risk factors in patients with COVID-19, we recommend early identification and correction of these factors, such as frequent measurement of the cuff pressure and, if possible, periodic evaluation of the tracheal mucosa with bronchoscopy to identify early precursor lesions of tracheoesophageal fistula. Regarding treatment, provide initial endoscopic management until optimal conditions for surgical management are reached. Endoscopic management should be selected according to the size and location of the fistula.

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INTRODUCTION

Tracheoesophageal fistulas (TEFs) are defined as abnormal communications between the esophagus and the trachea or bronchi, leading to the passage of oral and gastric secretions into the respiratory tract[1]. TEFs can be classified into two main categories: Congenital or acquired. The congenital form is frequently associated with type C esophageal atresia (85%), presenting in an isolated manner in 4% of cases. Characteristically, clinical manifestations of this condition develop early in life[2-4]. On the other hand, acquired TEFs mainly affect adults and are most frequently found in the cervicothoracic junction. TEFs can be malignant or benign. Each type constitutes approximately half of the acquired cases[4].

Malignant TEFs are a catastrophic complication of invasive neoplasms of the esophagus (squamous cell carcinoma), trachea, lung, or mediastinum[4-6]. On the other hand, benign fistulas mainly develop due to prolonged mechanical ventilation (through an endotracheal tube or tracheostomy); blunt trauma to the neck and chest; traumatic or surgical injury of the esophagus; granulomatous mediastinal infections; previous esophageal stents, or ingestion of foreign bodies/corrosives[5]. In patients undergoing invasive mechanical ventilation, some of the risk factors for TEFs include prolonged intubation, endotracheal cuff overinflation, excessive movement of the endotracheal tube (prone positioning), hypotension, diabetes mellitus, previous respiratory tract infections, use of steroids, and requiring nasogastric tube feeding, among others[7,8].

The most common clinical presentation of TEFs includes respiratory distress, dysphagia, cough after swallowing (ONO sign), malnutrition, and recurrent pulmonary infections. The severity of symptoms largely depends on their size and location[8,9]. A diagnosis should be made by combining characteristic findings on thoracic imaging (esophagogram and chest tomography with 3D reconstruction) and those on endoscopic studies such as bronchoscopy and upper endoscopy. These studies are also essential when planning the best treatment option for each patient[1,8,10,11].

The mean survival reported for patients with TEFs is less than 3 mo from the time of diagnosis. As such, adequate treatment should include an immediate multidisciplinary approach, including specialists in critical care, interventional pulmonology, gastroenterology, and thoracic surgery. Currently, there are few case reports regarding TEFs due to prolonged intubation in patients with coronavirus disease 2019 (COVID-19)[12-16]. We herein present a case series on patients with COVID-19 who develop TEFs and discuss diagnostic and therapeutic approaches.

CASE PRESENTATION

Chief complaints

Before creating this case series, we obtained informed consent from each patient or their legal guardians. We included patients who were admitted to a university hospital in the city of Bogotá, Colombia in the period between November 2020 and December 2021. We identified 14 adult patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia who developed TEFs as a complication

of prolonged mechanical ventilation.

We present the sociodemographic variables of the patients and relevant information on their past medical histories in Table 1. The average age was 53.5 years (range 38-72 years). Half of the sample was composed by men. Comorbidities were found in 85.7% of the patients, with the most frequent being obesity/overweight, diabetes mellitus, and systemic hypertension.

History of present illness

The clinical characteristics of the patients are shown in Table 2. The most common symptoms, which lead all patients to attend the emergency room, were cough and dyspnea. All of the subjects were diagnosed with severe pneumonia due to COVID-19. At least 64.2% presented with septic shock, requiring vasoactive support. All patients required invasive mechanical ventilation for more than 14 d. Acute respiratory distress syndrome (ARDS) was documented in 13 patients, and this variable was no available for assessment in one patient. All patients were treated with a steroid (dexamethasone: 6 mg s.c., q.d. for 10 d), and the steroid was prematurely stopped in one patient due to diabetic ketoacidosis during treatment. All patients received enteral nutrition through nasoenteral tubes.

The pressure of the endotracheal cuff was measured in only two patients (14.2%), being greater than 35 cmH_2O in both cases. TEFs were documented by endoscopic study of the upper digestive tract (100%) and in some cases with three-dimensional reconstruction of neck computed tomography (71.4%). All TEFs were found in the proximal esophagus, with an average distance of 16.7 cm from the dental arch, and the average diameter was 18.2 mm (range 3 mm-40 mm) (Figure 1).

All of the patients had bacterial infectious complications, including tracheitis (21.4%), pneumonia (64.2%), and bacteremia (21.4%). Therefore, they required treatment with broad-spectrum antibiotics leading to *Clostridioides difficile* infection in 14.2% of the sample. Six patients developed terminal acute kidney injury requiring renal replacement therapy. For the closure of TEFs, eight patients were taken to temporary or definitive endoscopic treatment: Four needed over the scope (OTS) clips, achieving successful endoscopic closure in two. Clip placement failed in one of the patients due to tissue fibrosis; a recurring defect was documented in another patient. Three patients received temporary management with a fully coated metallic stent (SEMS), managing to completely cover the defect. Hemoclips (TTS endoclips) were used in two patients. In one patient, with a 3 mm TEF, adequate closure of the defect was achieved; while in another patient, temporary reduction in diameter was achieved, allowing further management with an OTS clip (Figure 1). In six patients, a surgical approach was indicated given the location and size of the fistula. Surgical management was also provided to the patient with failure to therapy with the OTS clip, achieving successful correction of the defect. On follow-up, recurrence of TEFs was observed in only one patient treated with an OTS clip, and an increase in the size of the fistula was detected, for which surgical therapy was considered, successfully closing the defect. Despite the efforts made, 42.8% (6/14) died due to infectious complications, with two patients dying before receiving surgical management.

History of past illness

Comorbidities were found in 85.7% of the patients, with the most frequent being obesity/overweight (71.4%), diabetes mellitus (42.8%), and systemic hypertension (42.8%).

Physical examination

Half of the sample was composed by women with an average weight of 72.4 kg (body mass index [BMI] 27.4). The men had an average weight of 82 kg (BMI 26.6). The pressure of the endotracheal cuff was measured in only two patients (14.2%), being greater than 35 cmH_2O in both cases.

Imaging examinations

Three dimensional reconstruction of neck computed tomography was performed in 13 patients (92.8%), identifying the presence of a fistula in 71.4%. At the time of diagnosis, all patients were on invasive mechanical ventilation, so esophagogram was not performed in any of them.

FINAL DIAGNOSIS

TEFs were documented by endoscopic study of the upper digestive tract (100%) and in some cases with three-dimensional reconstruction of neck computed tomography (71.4%). All TEFs were found in the proximal esophagus, with an average distance of 16.7 cm from the dental arch, and the average diameter was 18.2 mm (range 3-40 mm) (Figure 1).

TREATMENT

For the closure of TEFs, eight patients were taken to temporary or definitive endoscopic treatment: Four

Table 1 Characteristics of patients with tracheoesofageal fistulas in 2020-2021

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total, *n* (%)
Age (years)	60	58	72	52	46	63	56	46	41	61	49	39	69	38	
Sex	M	F	M	F	F	F	F	F	M	M	M	M	M	F	
BMI	25.1	34.3	23.9	28.6	32	19.1	28	27	26	29.5	23	32	27.1	23.4	
Past medical history															
Diabetes mellitus	-	X	-	-	X	-	X	X	-	-	-	X	X	-	6 (42.8)
Systemic hypertension	-	-	X	-	-	X	X	X	-	-	-	X	X	-	6 (42.8)
Obesity/Overweight	X	X	-	X	X	-	X	X	X	X	-	X	X	-	10 (71.4)
Other	-	-	PC	-	-	H	-	-	H	AF	-	-	-	-	

BMI: Body mass index; M: Male F: Female BMI: Body mass index PC: Prostate cancer; H: Hypothyroidism AF: Atrial fibrillation.

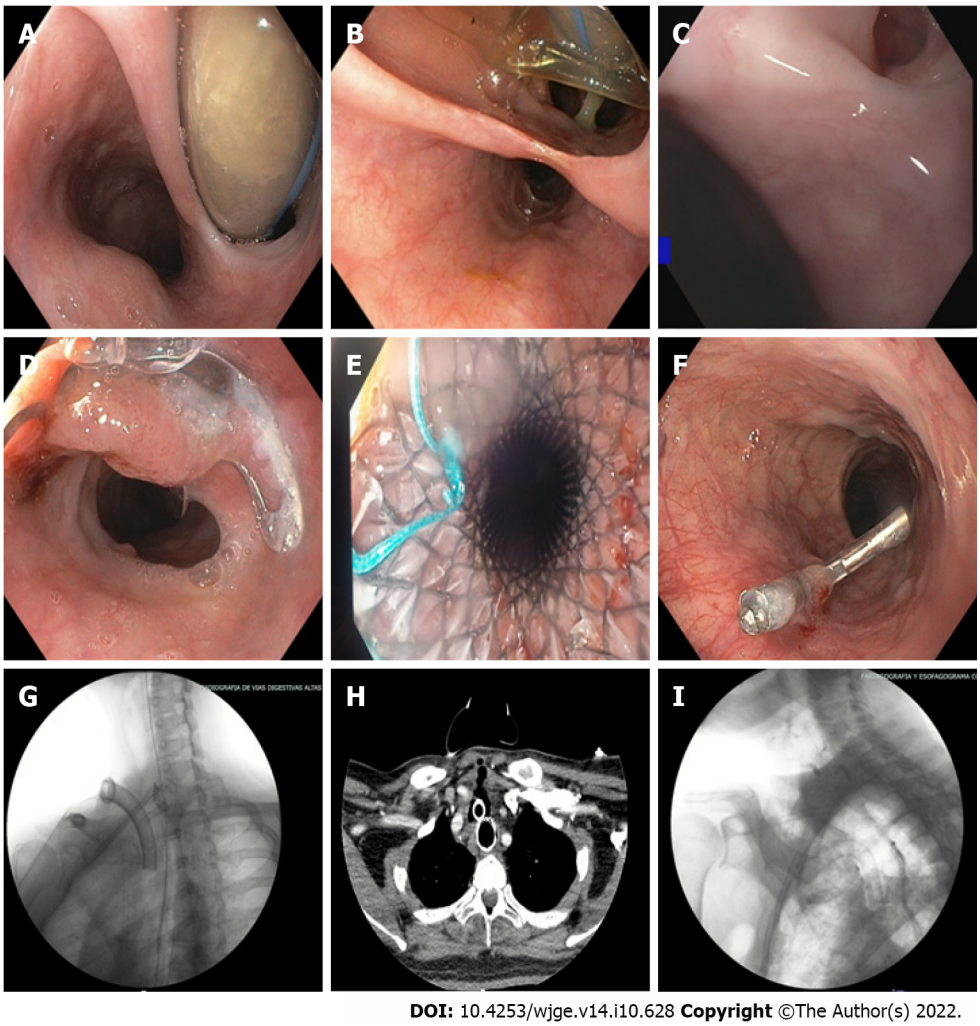

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Figure 1 Tracheoesophageal fistulas: Diagnosis and management. A: 20 mm tracheoesophageal fistula (TEF); B: 30 mm TEF; C: 3 mm TEF; D: Over the scope (OTS) clip closure (video 1); E: Closure with a partially coated self-expanding metal stent; F: Closure with a through-the-scope clip (TTS) endoclip; G: Esophagogram without leakage after OTS clip therapy; H: Axial computerized tomography showing closure of TEF with a fully covered SEMS; I: Esophagogram displaying TEF closure through TTS endoclips, with aspiration due to deglutition disorder. (Further pictures and video may be found as Supplementary material).

needed OTS clips, achieving successful endoscopic closure in two (video 1). Clip placement failed in one of the patients due to tissue fibrosis; a recurring defect was documented in another patient. Three patients received temporary management with a fully coated metallic stent (SEMS), managing to completely cover the defect. Hemoclips (TTS endoclips) were used in two patients. In one patient, with a

Table 2 Characteristics of patients with tracheoesophageal fistula in 2020-2021

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total, *n* (%)
Reason for consultation															
Fever	X	-	X	X	X	X	-	X	X	-	X	X	X	-	10 (71.4)
Cough	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Dyspnea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Clinical findings															
Viral pneumonia SARS CoV2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
SOFA	2	6	ND	4	8	ND	ND	10	ND	ND	ND	ND	6	ND	
Clinical course															
Invasive mechanical ventilation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
ARDS	X	X	ND	X	X	X	X	X	X	X	X	X	X	X	
Vasoactive	X	X	ND	X	X	X	ND	X	X	X	ND	ND	X	ND	
Shock	X	X	ND	X	X	X	ND	X	X	X	ND	ND	X	ND	
Steroids	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Dispositivo vía esofagica	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Cuff pressure measurement	-	-	-	X	-	-	-	-	X	-	-	-	-	-	2 (14.2)
Tracheostomy	X	X	-	X	-	-	X	-	X	X	X	X	-	X	9 (64.2)
Gastrostomy	X	-	-	X	-	X	X	-	X	X	X	X	-	X	9 (64.2)
Diagnosis															
Upper gastrointestinal endoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14 (100)
Axial computed tomography of the neck	X	X	X	X	X	X	N	X	-	N	X	X	N	X	13 (92.8)
Complications															
Tracheitis	X	-	-	-	-	-	-	-	-	-	-	X	X	-	3 (21.4)
Pneumonia	-	-	X	X	X	X	X	X	X	X	-	-	-	X	9 (64.2)
Bacteremia	-	X	-	-	-	-	-	-	-	-	X	-	-	X	3 (21.4)
Clostridioidal infection	-	-	X	-	-	-	-	-	-	-	-	-	-	X	2 (14.2)
Acute kidney injury	-	X	-	-	-	-	-	X	X	X	X	-	X	-	6 (42.8)
Treatment															
OTS clip	X	-	X	X	-	-	X	-	-	-	-	-	-	-	4 (28.5)
TTS endoclip	-	-	-	-	-	-	X	-	-	X	-	-	-	-	2 (14.2)
Self-expanding metallic stent	-	X	-	-	-	-	-	X	-	-	-	X	-	-	3 (21.4)
Surgery	X	-	-	X	-	X	-	-	X	-	X	X	-	X	7 (50)

TTS: Through-the-scope clip; OTS: Over-the-scope clip; ND: No data; SOFA: Sepsis organ failure assessment; ARDS: Acute respiratory distress syndrome; N: No fistula detected.

3mm TEF, adequate closure of the defect was achieved, while in another patient, temporary reduction in diameter was achieved, allowing further management with an OTS clip (Figure 1). In six patients, a surgical approach was indicated given the location and size of the fistula. Surgical management was also provided to the patient with failure to therapy with the OTS clip, achieving successful correction of the defect. On follow-up, recurrence of TEFs was observed in only one patient treated with the OTS clip, and an increase in the size of the fistula was detected, for which surgical therapy was considered, successfully closing the defect.

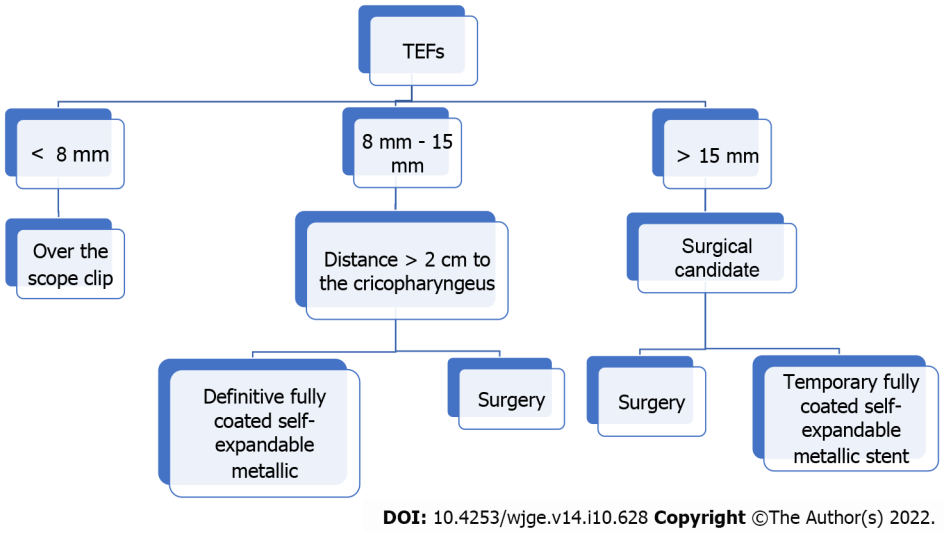

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Figure 2 Suggested treatment algorithm.

OUTCOME AND FOLLOW-UP

Despite the efforts made, 42.8% (6/14) of the patients died due to infectious complications, with two patients dying before receiving surgical management.

DISCUSSION

Acquired TEFs are a rare clinical entity, with incidence rates approaching 0.5%. Up to 75% of cases are due to trauma related to endotracheal cuff overinflation or prolonged mechanical ventilation[4,8,17]. The pressure exerted by the endotracheal tube cuff erodes the tracheal mucosa, leading to ischemic destruction of the tracheal cartilage, which creates a communication with the esophageal wall[4,8].

The current health situation, due to the SARS-CoV-2 pandemic, which significantly increased cases of severe pneumonia and ARDS, led to a parallel increase in TEFs associated with prolonged endotracheal intubation. We found that 14 out of 894 patients undergoing mechanical ventilation for severe COVID-19 pneumonia, developed TEFs (incidence 1.56%). In most patients, several risk factors were simultaneously found; these included prolonged mechanical ventilation, hypotension, steroid use, diabetes mellitus, obesity, and excessive movement of the endotracheal tube due to frequent position changes (supine-prone)[18]. We hypothesize that monitoring of the endotracheal cuff pressure was insufficient, possibly due to overcrowding in critical care units, as well as the exhaustion, anxiety, and depression developed by healthcare workers during the pandemic[19,20,21,22].

Spontaneous closure of TEFs is rare, and therefore requires the use of different treatment approaches, including endoscopic and surgical options[4,7,23]. Among the endoscopic options is the use of fully coated metallic stents (SEMS), OTS clips, TTS endoclips, and suture systems among others[24-27]. These procedures have allowed for high success rates (73%-83%) regarding closure of perforations, leaks, and gastrointestinal fistulas[28]. However, due to a low incidence of TEFs, no consensus guidelines on the management of this entity currently exist, particularly concerning patients with SARS-CoV-2 infection. It has been reported that mechanical ventilation increases the risk for suture dehiscence. Furthermore, comorbidities and the critical condition of patients with severe COVID-19 pneumonia usually lead to deferral of surgical procedures until after mechanical ventilation withdrawal. This is why considering endoscopic interventions as initial management in critically ill patients with tracheoesophageal fistula associated with mechanical ventilation due to COVID-19 should be sought.

We present a treatment algorithm for this group of patients in Figure 2. Our approach is determined by the size and location of the fistula, using OTS clips for defects below the size of 8 mm. For lesions between 8 and 15 mm, we suggest to use SEMS as long as the fistula is more than 2 cm distal to the cricopharyngeus where the stent can be properly fixed. In lesions larger than 15 mm, we propose upfront surgical treatment, as well as when the fistulas are less than 2 cm from the cricopharyngeus (because at this distance the stent may lead to foreign body sensation). When the patient is not a good surgical candidate and has lesions larger than 15 mm located more than 2 cm away from the cricopharyngeus, a fully SEMS can be placed as bridging therapy until the patient becomes stable and in better condition for surgical treatment. Although we have a small sample size, to the best of our knowledge, this is the first study to illustrate the management of this type of patients in the context of the coronavirus pandemic.

CONCLUSION

Due to the significant increase in diagnosis of TEFs in patients with severe pneumonia due to COVID-19, and the high frequency of risk factors for TEFs in these patients, we recommend early identification and prevention of these conditions, in addition to frequent measurement of the endotracheal cuff pressure. If possible, we recommend periodic evaluation of the tracheal mucosa by bronchoscopy to identify early lesions that could lead to the development of TEFs. Regarding treatment, we suggest providing initial endoscopic management in small fistulas (below 15 mm) or until optimal conditions for surgical management are met (if larger than 15 mm). Definitive endoscopic treatment may be offered according to the size and location of the fistula.

FOOTNOTES

Author contributions: Gomez M was responsible for the revision of the manuscript for important intellectual content; Gallego D and Ruiz O reviewed the literature and contributed to manuscript drafting; all authors were the patient's gastroenterologists; all authors issued final approval for the version to be submitted.

Informed consent statement: Informed consent was obtained from each of the patients or their legal representatives.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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CASE REPORT

Hemostasis of massive bleeding from esophageal tumor: A case report

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Abstract

BACKGROUND

Esophageal cancer is a common type of cancer and serious bleeding from esophageal tumors can occur in routine clinical practice. The arrest of bleeding from esophageal tumor is not a trivial task, which can sometimes require non-standard solutions. We report a case of successful hemostasis of massive bleeding from esophageal tumor performed by a novel two-balloon catheter inserted endoscopically, with a local hemostatic treatment applied.

CASE SUMMARY

A 36-years old male patient with advanced esophageal cancer developed bleeding from the tumor following endoscopic stenting with a self-expanding metal stent. Due to the ineffectiveness of standard approaches, after a medical conference, the patient was treated with a novel method based on the use of a two-balloon catheter creating an isolated area in esophagus and locally dispersing hemostatic polysaccharide powder inside the isolated interior. Hemostasis was successful and subsequent endoscopic examination revealed the presence of organized clot and localized defect, which was coagulated in a planned manner.

CONCLUSION

The authors present a new catheter-based method of hemostasis of esophageal tumor bleeding.

Key Words: Esophageal cancer; Esophageal bleeding; Two-balloon catheter; Endoscopic hemostasis; Hemostatic polysaccharide powder; Case report

Core Tip: We describe a novel method of managing difficult-to-treat condition using an original device/catheter that we developed. Our experience of managing gastrointestinal and, in particular, esophageal bleeding suggests that treatment of such conditions is a major challenge with no readily available and reliably working solutions. Success depends on multiple factors, all subject to limitation of time available for decision-making and application of treatment methods. A major advantage of our method is its ease of use and ability to be deployed by physicians of all levels and in all hospital settings. We believe that our method can help save many lives.

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INTRODUCTION

Various stages of dysphagia are common complications of esophageal cancer. Stenting of esophageal tumors is a standard method of treatment and palliative care. Placement of a self-expandable metal stent is required, on the one hand to facilitate oral nutrition and on the other hand as the first standard step of treatment pre-empting neoadjuvant chemotherapy with brachytherapy[1,2]. At the same time, placement of a stent can lead to the development of various complications, the frequency of which can reach up to 50%[3]. The most common are esophageal perforation, fistula, stent migration, and bleeding [4,5]. The incidence of bleeding after stenting is not high and varies from 1% to 12%[6,7]. However, the volume of bleeding if it occurs is often massive and is associated with high mortality[6,7]. Due to the fact that this complication is rare, and its course is extremely aggressive, the experience of managing this group of patients is limited. The recommendations are nonsystematic in nature and one should be prepared for various scenarios, from the application of various hemostatic remedies and transfusion of blood components to angiographic methods to stop the bleeding. The unfavorable outcome of this complication can be caused by a stent itself that interferes with verification of the source of bleeding, by pathological hypervascularization of a tumor, rich blood supply of the esophagus, including from esophageal arteries stemming from the descending aorta, and by a limited amount of time available to help a patient[6-9].

Analysis of the literature suggests that time is the main factor in the unsatisfactory result of trying to achieve hemostasis during the first wave of bleeding. The time spent on patient admission and delays in identifying the source of bleeding, trying various options of endoscopic hemostasis, switching to endovascular methods, all negatively affect the outcome of treatment. To counter this, a method has been developed that consists of isolating the source of bleeding, in this case the part of the esophagus with a tumor, from other parts of the gastrointestinal tract, with the possibility of delivering hemostatic agents into it while maintaining the connectivity between the parts of esophagus proximal and distal to the isolated region. The latter feature enables concurrent and continuous drainage of the proximal part and administration of solutions and enteral nutrition. This approach achieves several important effects. First, it allows one to mechanically create an isolated area with high pressure in which blood, clots, and coagulation factors facilitate hemostasis. Second, it enables localized delivery of hemostatic agents such as polysaccharide hemostatic powders. Third, by maintaining functional connectivity of the gastrointestinal tract, the method allows both for essential nutritional support and provision of fluids, and for sufficient exposure time to achieve hemostasis.

CASE PRESENTATION

Chief complaints

Vomiting with blood, melena, weakness, an episode of loss of consciousness.

History of present illness

A 36-year-old male patient was admitted on an emergency basis on November 14, 2021, with manifestation of gastrointestinal bleeding. At the time of admission, the degree of blood loss, according to the changes in the level of hemoglobin, erythrocytes and hematocrit, was assessed as moderate.

History of past illness

When collecting an anamnesis, it was established that for the first time the dysphagia was observed in

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Figure 1 X-ray of esophagus revealing a filling defect.

September 2021. An X-ray investigation performed at the time revealed changes characteristic of a tumor of the gastroesophageal junction (Figure 1). The patient categorically refused further examination and treatment and was discharged. Later he was followed up at the oncology clinic, and on October 29 diagnosed with cancer of gastroesophageal junction, type II according to Siewert classification, stage IVB, Grade 2, dMMR/MSI-h-negative, HER2-negative adenocarcinoma. Concomitant diseases: obesity class III, essential hypertension. On November 10, endoscopic stenting of esophagus was performed to resolve dysphagia. The patient was discharged on November 13, 2021.

Personal and family history

There was no personal and family history of cancer.

Physical examination

At the time of admission, blood pressure was 80/40 mmHg and heart rate was 114 beats/min.

Laboratory examinations

Blood analysis demonstrated high volume of loss, with erythrocyte count 2.1 mln cells/uL, hemoglobin 79 g/L, and hematocrit 31.0%.

Imaging examinations

Endoscopic examination revealed that there was ongoing bleeding from under the partially covered esophageal stent (Figure 2). It was however not possible to clearly establish the localization of the source of bleeding.

MULTIDISCIPLINARY EXPERT CONSULTATION

Given the severity and urgency of situation, a multidisciplinary meeting was held, which included surgeons, endoscopists and anesthesiologists.

FINAL DIAGNOSIS

Cancer of the gastroesophageal junction, type II according to Siewert classification, stage IVB, Grade 2, dMMR/MSI-h-negative, HER2-negative adenocarcinoma. Complications: severe esophageal bleeding. Concomitant diseases: obesity class III and essential hypertension.

TREATMENT

Both standard intravenous hemostatic therapy and blood component transfusion were administered. An attempt to perform endoscopic hemostasis by electrocoagulation of the tumor failed to achieve positive results. It was decided that due to the impossibility of achieving hemostasis using standard methods and further deteriorating condition of the patient, it was advisable, according to vital indications, to use the isolation method and locally introduce a polysaccharide powdered hemostatic

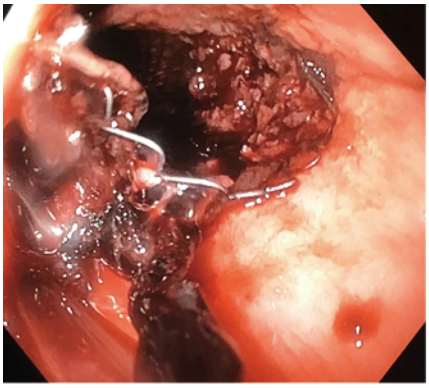

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Figure 2 Endoscopic view of bleeding with visualization of uncovered part of the stent. There were visible signs of tumor growth.

agent. The two-balloon catheter was inserted endoscopically into the stomach past the stent, so that the tumor site with the source of bleeding were located between the balloons. Balloons were inflated isolating the area of bleeding, and hemostatic powder was injected though the catheter opening located between the balloons and dispersed inside the isolated interior. The procedure stopped the bleeding, as demonstrated by normalization of hemodynamic parameters and absence of retrograde flow of blood through the main channel of the catheter. Over the next day, there was no sign of bleeding recurrence, which was supported by stable levels of hemoglobin and erythrocyte count. On November 15, the day after hemostasis, the catheter was removed, and repeated endoscopic procedure was performed in order to identify the source of bleeding and to reposition the esophageal stent. A 1.5-cm long defect with an organized clot was detected in the gastroesophageal junction (Figure 3). Argon plasma coagulation was performed after which the same stent was repositioned and fixed. Fluoroscopy performed on November 18 showed that stent's position was adequate, the contrast medium freely entered the stomach, and there were no streaks or signs of stent migration (Figure 4). No recurrence of bleeding was observed, and the patient was discharged on November 18 in adequate condition to continue treatment at the oncology clinic.

OUTCOME AND FOLLOW-UP

After 4 mo of follow-up on March 9, 2022, patient was hospitalized with recurrent dysphagia. Endoscopy of the upper part of the stent revealed tumor overgrowth and infiltration with stenosis of the esophagus. Endoscopic ablation with tumor coagulation and recanalization of the esophagus was performed successfully. Two days after the procedure, clinical signs of dysphagia disappeared, as confirmed by controlled esophageal fluoroscopy, and the patient was discharged.

DISCUSSION

Bleeding after stenting of esophageal cancer is a severe complication with a high rate of mortality. Most often it develops in the first 2 wk after manipulation[8,9]. The main reasons include mucosal trauma caused by the free uncovered part of the stent during active esophageal peristalsis and increased pressure on the wall of the organ at the time of its expansion by the stent, leading to necrotic changes [10]. Since the esophagus is well supplied with blood, the bleeding is often massive. The presence of a stent hampers identification of the source of bleeding, and prevents application of argon plasma coagulation, injection of adrenaline or clipping. Large number of collateral blood vessels and segmental type of blood supply of the esophagus are the reason why many authors recommend supplementing endoscopic approaches with endovascular methods of hemostasis, which nevertheless often fail to achieve the desired effect[8-10]. It is important to have a wide range of methods available for both identification and tackling of the source of bleeding. In clinical practice however, resources are often limited and implementation of extensive care is associated with loss of time, which in this case is critical. Presence of disseminated tumor and poor somatic status of a patient can also play an important role, limiting the surgeon's options.

The method of hemostatic treatment described here allows for localization of the source of bleeding by isolating it from other parts of the gastrointestinal tract. At the same time, it does not require identification of precise location of the site of bleeding. The method implements four hemostatic approaches: (1) Applying pressure on the submucosal vessels by the inflated balloons; (2) tamponade of the source

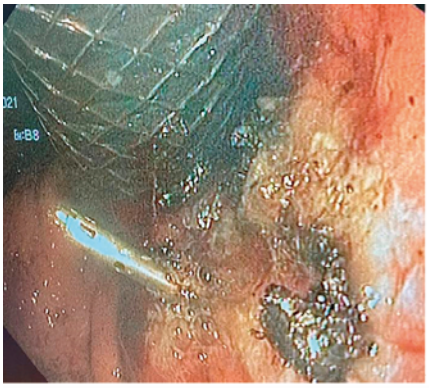

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Figure 3 View of a clot in the gastroesophageal junction after stent removal.

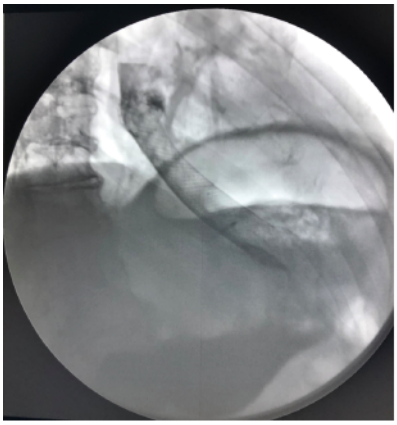

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Figure 4 X-ray of esophagus. Correct location of the stent in the gastroesophageal junction was visualized.

of bleeding by blood clots; (3) targeted delivery of hemostatic agents to the bleeding site; and (4) prevention of migration of hemostatic agents and blood clots to other parts of the gastrointestinal tract due to peristalsis. The latter prolongs exposure to hemostatic agents, which is enhanced by the ability of the two-balloon catheter used in the procedure to preserve connectivity of the gastrointestinal tract and to remain in place long enough to achieve the desired hemostatic effect.

CONCLUSION

Availability of a fast and simple method for stopping bleeding from a tumor in the esophageal lumen, which does not require a high level of specialist training, is easy to perform and that provides long-term hemostasis and ability to administer enteral nutrition and drain the upper part of the esophagus, will help save time and improve the quality of care for this group of patients. While the present case is focused on esophageal bleeding, the method proposed could be applied to treating bleeding in other parts of the gastrointestinal tract.

FOOTNOTES

Author contributions: Kashintsev AA, Anisimov SV, Granstrem OK, Kutumov EB, Nadeeva AA and Proutski V designed the study; Kashintsev AA, Rusanov DS, Antipova MV, Kokhanenko NY and Medvedev KV performed the study; Kashintsev AA, Anisimov SV, Granstrem OK, and Proutski V analyzed the results and wrote the manuscript; all authors have read and approve the final manuscript.

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CASE REPORT

Cronkhite-Canada syndrome: First case report from Egypt and North Africa

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Abstract

BACKGROUND

Gastrointestinal (GI) polyposis is a rare condition in GI diseases. To date about 500 cases of Cronkhite-Canada syndrome (CCS) have been reported worldwide.

CASE SUMMARY

We report a 60-year-old female patient who presented with dyspepsia, abdominal pain, and weight loss of 1-year duration. Her physical examination showed alopecia and onychodystrophy. Upper endoscopy revealed diffuse markedly thickened gastric mucosa involving the whole stomach with thickened gastric rugae and numerous polypoidal lesions. Histopathological examination showed marked hyperplasia of the foveolar glands with inflammatory cell infiltration. Endoscopic ultrasound showed a significantly hypertrophic mucosa and muscularis mucosa, while the submucosa and the muscularis propria were spared, favouring its benign nature. Colonoscopy showed multiple sessile polyps scattered at different parts of the colon. Histopathological examination revealed tubular adenomatous polyps with low-grade dysplasia. Differential diagnoses included CCS, Menterier disease (MD), other polyposis syndromes, lymphoma, amyloidosis, and gastric malignancies. The presence of alopecia, nail dystrophy, GI polyposis, markedly

thickened gastric mucosa and folds, abdominal pain, weight loss, and marked foveolar gland hyperplasia; all was in favour of CCS. Lymphoma was excluded due to sparing of the muscularis propria. The presence of colonic polyps and antral and duodenal infiltration, and the absence of hypoproteinaemia decreased the possibility for MD.

CONCLUSION
The patient was diagnosed as having CCS.

Key Words: Gastrointestinal polyposis; Thickened gastric mucosa; Cronkhite-Canada syndrome; Case report

Core Tip: Cronkhite-Canada syndrome (CCS) is a rare acquired polyposis with unknown aetiology. To date about 500 cases have been reported worldwide. We herein report an Egyptian patient with CCS. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa. Cases presenting with gastrointestinal (GI) polyposis and marked thickened gastric mucosa and folds represent challenging cases and diagnostic dilemmas. The diagnosis was based on history, physical examination, endoscopic findings, and histology. CCS is typically characterized by GI symptoms, such as diarrhea and skin changes (*e.g.*, alopecia, pigmentation, and nail dystrophy), while endoscopic features include diffuse polyps throughout the entire GIT, except for the esophagus. Pathological types of polyps in CCS mainly include inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps. CCS can be complicated by many diseases and has a malignant tendency with a high mortality rate. Till now, there has been no uniform standard treatment for CCS.

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INTRODUCTION

Cronkhite-Canada syndrome (CCS) is one of the rarest nonhereditary diseases[1], and its exact aetiology is still unknown[2], with around 500 cases having been described in the literature[3]. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa.

Patient with CCS usually presents with gastrointestinal (GI) symptoms such as abdominal pain, weight loss, and diarrhea, or with other symptoms such as onychodystrophy, alopecia, hyperpigmentation of the skin, and rarely vitiligo[4]. GI polyposis is the main endoscopic feature in CCS, which is commonly non-neoplastic and rather inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps in nature[5]. Moreover, some CCS cases may develop gastric and colorectal malignancies during the disease course[4].

CASE PRESENTATION

Chief complaints

A 60-year-old female patient presented with dyspepsia, abdominal pain, and weight loss of 1-year duration.

History of present illness

The patient denied other GI or anaemic symptoms. She was a non-smoker and did not drink alcohol.

History of past illness

The patient's past medical history was free apart from prolonged proton-pump inhibitor (PPI) intake.

Personal and family history

There was no family history of gastrointestinal polyposis or colorectal malignancy.

Physical examination

The physical examination was unremarkable apart from alopecia (Figure 1A) and onychodystrophy (Figure 1B).

Laboratory examinations

The patient's laboratory profile was within normal limits including a full complete blood picture (CBC), chemistry, serum albumin, serum calcium, urine analysis, antinuclear antibody (ANA), and IgG-4.

Imaging examinations

Oesophago-gastro-duodenoscopy (OGD) revealed diffuse markedly thickened gastric mucosa involving the whole stomach (fundus, body, and antrum), with thickened and tortuous gastric rugae, and numerous polypoidal lesions (3-10 mm in diameter), with a hyperaemic mucosa, and to a lesser extent down to the duodenal bulb and second part of the duodenum (Figure 2A and B). Multiple conventional biopsies were taken, and polypectomy was done for the large polyps for histopathological examination. Biopsies showed marked hyperplasia and cystic dilation of foveolar glands with inflammatory cell infiltration including eosinophils, hyperplastic polyps, chronic gastritis, and *Helicobacter pylori* (*H. pylori*) infection with no atypia or malignancy (Figure 3). IgG4-immunohistochemistry showed a very faintly positive signal.

Endoscopic ultrasound was done later and showed a significantly hypertrophic mucosa and muscularis mucosa, while the submucosa and the muscularis propria were spared, favouring its benign nature. Wall thickness was up to 8-10 mm (normal wall thickness is up to 4 mm) (Figure 2C).

Colonoscopy showed multiple variable-sized, sessile, and pedunculated polyps (~15), scattered at different parts of the colon. Snaring of the large polyps was done after submucosal injection (Figure 2D and E), and histopathological examination showed typical features of benign juvenile-like and hamartomatous polyps without dysplastic changes, while pathology of other polyps revealed tubular adenomatous polyps with low-grade dysplasia.

Both push enteroscopy and terminal ileoscopy showed no polyposis with a normal mucosa in the 3rd and 4th portions of the duodenum, the proximal jejunum, and the terminal ileum.

Computerized tomography (CT) scan of the abdomen & pelvis with oral and intravenous (IV) contrast revealed mild circumferential mural thickening of the gastric wall.

FINAL DIAGNOSIS

The patient was diagnosed as having CCS.

TREATMENT

The patient started a sequential therapy for *H. pylori* infection with complete eradication, followed by a proton pump inhibitor (40 mg once daily), prednisolone (30 mg/d), and mesalazine (500 mg QID) for 6 mo.

DISCUSSION

In our case, the following differential diagnoses were raised and discussed with our gastroenterologists: CCS, MD, other polyposis syndromes (such as familiar adenomatous polyposis, Gardner syndrome, juvenile polyposis, Peutz-Jeghers syndrome, and Turcot syndrome), lymphoma, amyloidosis, duodenal gastric heterotopia, and gastric malignancies.

The final diagnosis was based on the medical history, physical examination, endoscopic findings, and the histopathological examination. The presence of anomalies of ectodermal tissues (such as alopecia and nail dystrophy), gastrointestinal polyposis (hamartomatous and adenomatous polyps), markedly thickened gastric mucosa and folds, abdominal pain, weight loss, and marked foveolar gland hyperplasia; all was in favour of the CCS. On the other hand, there was no protein-losing enteropathy, diarrhea, hypoalbuminaemia, or skin pigmentation.

Lymphoma was excluded due to sparing of the muscularis propria. Furthermore, markedly thickened gastric mucosa and folds and the histopathological examination which revealed marked foveolar gland hyperplasia were consistent with MD. In addition, abdominal pain and weight loss are common presentation of MD, but the presence of colonic polyps, and antral and duodenal infiltration, and the absence of hypoproteinaemia decreased the possibility for MD.

The patient started a sequential therapy for *H. pylori* infection with complete eradication, followed by a proton pump inhibitor (40 mg once daily), prednisolone (30 mg/d), and mesalazine (500 mg QID) for 6 mo.

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Figure 1 Physical examination. A: Alopecia; B: Onychodystrophy.

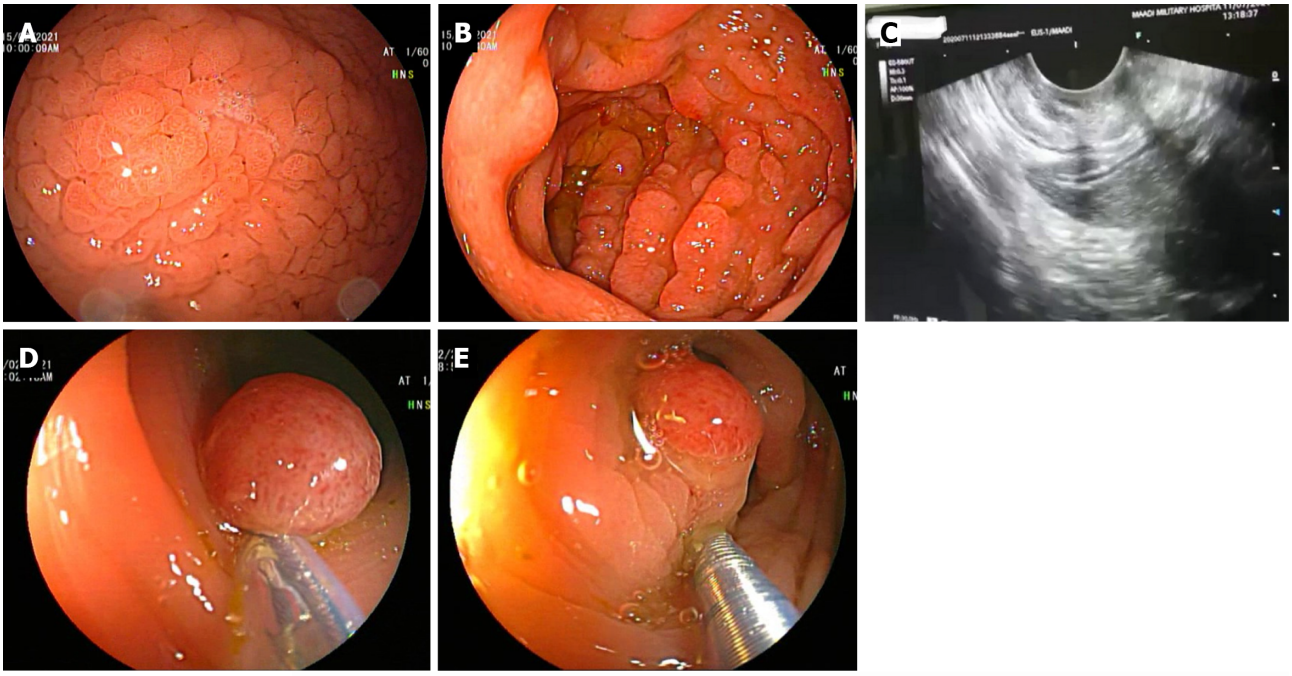

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Figure 2 Endoscopy. A and B: Upper endoscopy revealed a diffuse markedly thickened gastric mucosa with numerous polypoidal lesions; C: Endoscopic ultrasound revealed a significantly hypertrophic mucosa and muscularis mucosa, but sparing of the submucosa and the muscularis propria; D and E: Colonoscopy showed multiple variable-sized, sessile, and pedunculated polyps, which were removed by snare polypectomy.

Common complications of CCS include anemia, intussusception, rectal prolapse, and GI bleeding, as well as other less common ones such as recurrent severe acute pancreatitis, myelodysplastic syndrome, cecal intussusception, portal thrombosis, membranous glomerulonephritis, and osteoporotic fractures that may result from malabsorption of calcium or prolonged glucocorticoid therapy or both. The most serious complication is malignancy; however, the incidence of CCS-related cancer is estimated to be 5%-25%, especially gastric and colon cancer[6].

The follow-up endoscopies (OGD and colonoscopy) after 6 and 12 mo of treatment showed significant remission with a reduced number of gastric and colonic polyps and regression of hypertrophic gastric folds (Figure 4). Consequently, the patient's clinical condition was markedly improved, and the prednisolone dose was reduced gradually to 7.5 mg/d, but the mesalazine dose remained the same.

There is a tendency of malignant transformation or coexistence of gastrointestinal malignancies in patients with CCS. Therefore, endoscopic documentation of regression in CCS is important despite the

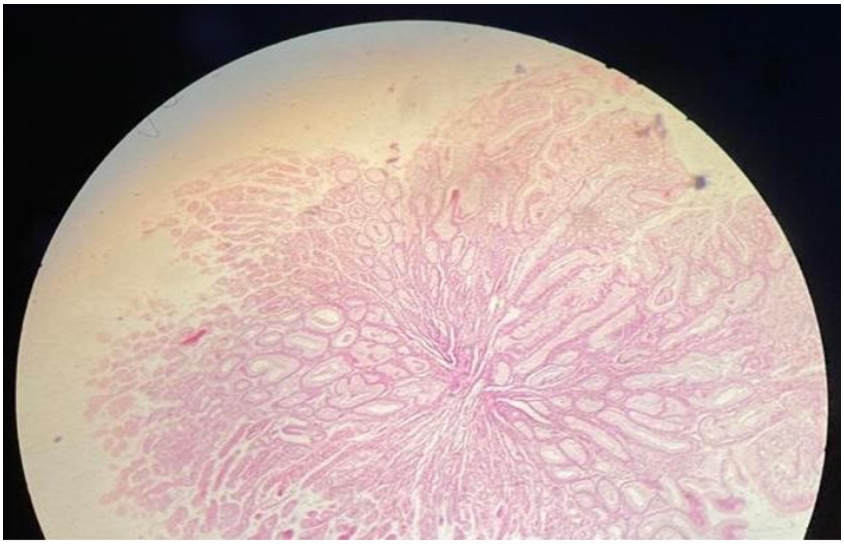

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Figure 3 Histopathological examination showed marked hyperplasia and cystic dilation of foveolar glands with inflammatory cell infiltration including eosinophils, chronic gastritis, and *Helicobacter pylori* infection with no atypia or malignancy.

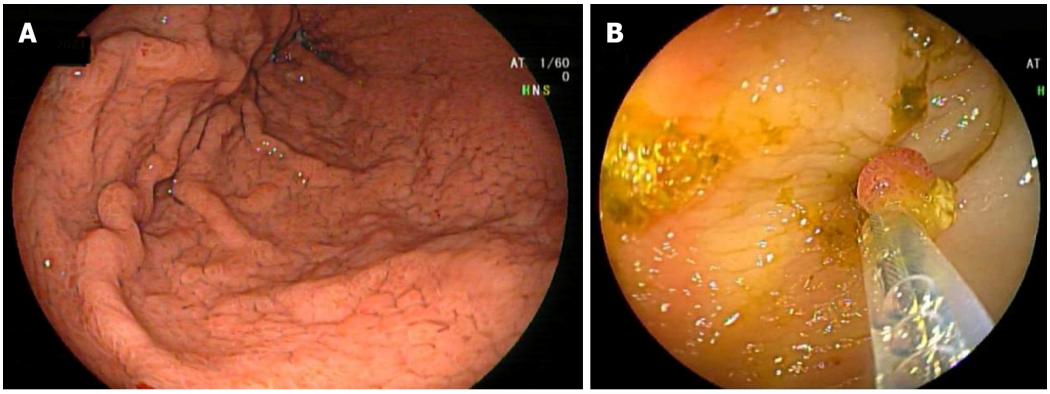

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Figure 4 Follow-up endoscopies after 6 mo and 12 mo of treatment showed significant remission with a reduced number of gastric and colonic polyps and regression of hypertrophic gastric folds. A: Upper endoscopy; B: Colonoscopy.

lower incidence of CCS-related cancer in remission patients. Therefore, the comprehensive endoscopic annual surveillance either *via* chromoendoscopy or directed biopsy from irregular polyps, to exclude pre-cancer lesions before development of invasive carcinoma is mandatory; however, there are still no recommended guidelines to be followed[7].

Nutritional support, electrolytes, and mineral and vitamin supplementation remain the cornerstone in treatment of CCS beside antibiotics and corticosteroids; however, the definitive treatment is still unknown[4,7].

Till now, there is still much that needs to know about this syndrome. In this context, the most important issue is to maintain treatment monitoring and provide appropriate measure to prevent relapse[8].

CONCLUSION

CCS is a form of uncommon, acquired polyposis with obscure aetiology. To date around 500 cases have been reported all over the world. Most of CCS cases were reported from Japan, and to our knowledge, our case is the first case reported from Egypt and North Africa. CCS is generally characterized by GI symptoms, such as diarrhea and skin changes (*e.g.*, alopecia, skin pigmentation, and onychodystrophy), while GI polyposis is the main endoscopic feature in CCS, which is commonly non-neoplastic and mainly include inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps. CCS has a malignant potential, and some cases may develop gastric and colorectal malignancies during the disease

course. Till now, there is no uniform standard treatment for CCS.

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FOOTNOTES

Author contributions: Alzamzamy A contributed to data acquisition, analysis, and interpretation, all endoscopies, and drafting of the manuscript; Aboubakr A, Okasha H, and Othman M edited the manuscript and supervised the research; Alzamzamy A and Abdelatif A wrote the manuscript; Elsayed H contributed to the histopathology work and result analysis; Elkholy S, Wahba M, and Alboraie M contributed to data acquisition, analysis, and interpretation; all authors approved the final version of the manuscript.

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CASE REPORT

Gastrointestinal histoplasmosis complicating pediatric Crohn disease: A case report and review of literature

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Abstract

BACKGROUND

Infection with *Histoplasma capsulatum* (*H. capsulatum*) can lead to disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and diarrhea which may mimic inflammatory bowel disease (IBD).

CASE SUMMARY

We report a case of 12-year-old boy with presumptive diagnosis of Crohn disease (CD) that presented with several months of abdominal pain, weight loss and bloody diarrhea. Colonoscopy showed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon. Histologic sections from the colon biopsy revealed diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates, and occasional non-necrotizing granulomas. Grocott-Gomori's Methenamine Silver staining confirmed the presence of numerous yeast forms suggestive of *Histoplasma* spp., further confirmed with positive urine *Histoplasma* antigen (6.58 ng/mL, range 0.2-20 ng/mL) and serum immunoglobulin G antibodies to *Histoplasma* (35.9 EU, range 10.0-80.0 EU). Intravenous amphotericin was administered then transitioned to oral itraconazole. Follow-up computed tomography imaging showed a left lower lung nodule and mesenteric lymphadenopathy consistent with disseminated histoplasmosis infection.

CONCLUSION

Gastrointestinal involvement with *H. capsulatum* with no accompanying respiratory symptoms is exceedingly rare and recognition is often delayed due to the overlapping clinical manifestations of IBD. This case illustrates the importance of excluding infectious etiologies in patients with "biopsy-proven" CD prior to initiating immunosuppressive therapies. Communication between clinicians and pathologists is crucial as blood cultures and antigen testing are key studies that should be performed in all suspected cases of histoplasmosis to avoid misdiagnosis and inappropriate treatment.

Key Words: Crohn disease; Disseminated histoplasmosis; Endoscopy; Colon; Inflammatory bowel disease; Immunosuppression; Case report

Core Tip: Impaired cell-mediated immunity is known to increase the risk for disseminated histoplasmosis and has been described in the setting of Crohn disease (CD) treated with immunosuppressant agents. Endoscopically, the appearance of histoplasmosis varies and includes features of inflammatory mucosal changes. Increasing awareness of this condition is critical to avoid misdiagnosis and inappropriate treatment, particularly in the setting of underlying CD. While no specific recommendations are available, immunosuppressive therapy may be safely initiated in some cases when there appears to be effective response to antifungal therapy and the patient can be monitored closely.

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INTRODUCTION

Histoplasmosis is an infection caused by inhalation of spores from the fungus *Histoplasma capsulatum* (*H. capsulatum*), found in soil enriched with bird and bat droppings and is endemic to the central and eastern states, prevalent in the Ohio and Mississippi River Valleys[1,2]. Clinical manifestations are typically self-limiting in immunocompetent children, whereas immunocompromised children are likely to present with more severe or disseminated disease and may be indistinguishable from malignancy or tuberculosis[3,4]. Single-organ histoplasmosis is rare, primarily affecting the lungs, occasionally lymph nodes, liver, bone marrow, skin and mucosal membranes[5-8]. While the literature contains many reports of disseminated histoplasmosis reminiscent of Crohn disease (CD) radiographically and endoscopically in immunocompromised patients, there are relatively few reports of symptomatic gastrointestinal histoplasmosis occurring in immunocompetent patients. The most commonly involved sites are the terminal ileum and the colon[9]. We report a case of an immunocompetent pediatric patient presenting with possible disseminated histoplasmosis after presumed initial diagnosis of CD. Early detection is critical to avoid treatment with immunosuppressive therapy and potential complications.

CASE PRESENTATION

Chief complaints

The patient is a 12-year-old boy who presented with several months of abdominal pain, weight loss, and bloody diarrhea.

History of present illness

The patient experienced abdominal pain, weight loss, and bloody diarrhea and was referred for upper and lower GI endoscopy with biopsy.

History of past illness

His medical history was remarkable for several mild and self-limiting respiratory illnesses with non-productive cough. The most recent episode occurred fourteen months prior to his current presentation.

Personal and family history

No notable personal or family medical history.

Physical examination

Unremarkable physical examination.

Laboratory examinations

Esophagogastroduodenoscopy was performed and revealed focally ulcerated gastric mucosa and several inflammatory polyps arising within the second and third portions of the duodenum.

Colonoscopy revealed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon (Figure 1). An erythematous region containing shallow ulcers was identified at the hepatic flexure. Multiple biopsies were taken from throughout the colon. A presumptive diagnosis of CD was made, methylprednisolone (40 mg/kg/d, IV) was administered and the patient was then discharged on oral prednisone (40 mg, QD) and oral mesalamine (1000 mg, TID).

Histologic examination of an H&E-stained colonic biopsy revealed a diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates and occasional non-necrotizing granulomas (Figure 2A-C). Grocott-Gomori's methenamine silver (GMS) and Periodic acid-Schiff stains confirmed the presence of numerous yeast forms morphologically suggestive of *H. capsulatum* (Figure 2D and E), further confirmed with positive urine *Histoplasma* antigen (6.58 ng/mL, positive range 0.2-20 ng/mL) and serum immunoglobulin G (IgG) antibodies to *Histoplasma* (35.9 EU, positive ≥ 10.0 EU).

Given the unusual nature of the histoplasmosis infection, an immunological workup was initiated and revealed profound hypogammaglobulinemia: Serum IgG 94 mg/dL (range 638-1453), IgM 9 mg/dL (range 56-242), and IgA 40 mg/dL (range 45-285) as well as CD8 lymphopenia (253/mm^3, range 331-1445). Genetic testing was ordered for inborn error of immunity using Invitae Primary Immunodeficiency Panel and one pathogenic variant was identified in CD40LG c.43del (pThr15Leufs*7), associated with X-linked hyper-IgM syndrome (XHIGM) and two likely pathogenic variants in TNFRSF13B c.310T>C (p.Cys104RG) (homozygous), associated with recessive common variable immunodeficiency (CVID).

Imaging examinations

Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a calcified left lower lobe lung nodule with associated hilar lymphadenopathy, diffuse colitis with wall thickening of the distal small bowel through the cecum, abdominal lymphadenopathy, and abnormal-appearing adrenal glands, likely related to disseminated histoplasmosis infection.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was isolated gastrointestinal histoplasmosis complicating newly diagnosed, presumed CD.

TREATMENT

An induction regimen of liposomal amphotericin was administered (3 mg/kg/d, IV) followed by 1 year of oral itraconazole (200 mg, BID) and treatment with oral mesalamine (1000 mg, TID) to maintain endoscopic remission with plans for endoscopy and colonoscopy in the future after trailing off medication at 6 mo.

OUTCOME AND FOLLOW-UP

Ongoing follow-up is planned for diagnostic evaluation of CD and the treatment plan includes maintaining clinical improvement and *Histoplasma* antigen clearance. Decisions on whether to initiate treatment for CD are pending as duration of antifungal therapy and safety of immunosuppressive therapy are to be determined. To date, our patient has completed 5 mo of a 12-mo course of antifungal therapy and is maintained on mesalamine until follow-up endoscopy and colonoscopy. The patient's symptoms have largely resolved and remain stable after 5 mo of follow-up.

DISCUSSION

Gastrointestinal involvement commonly occurs as part of disseminated histoplasmosis; however isolated colonic involvement with lack of respiratory symptoms is rare[10]. Histoplasmosis can occur at any age. Nonspecific clinical manifestations of gastrointestinal involvement such as abdominal pain, fever, weight loss, and diarrhea are variably present and may only be mild[6,10,11]. Immunocompromised patients are at increased risk of developing disseminated disease and may experience complications such as bleeding or intestinal obstruction more readily than immunocompetent individuals. A high index of suspicion is required for diagnosing histoplasmosis and the gold standard for diagnosis includes isolation of the fungus in blood culture and antigen testing in suspected cases, as utilizing both serum and urine consistently provides the highest sensitivity for detection. Testing for

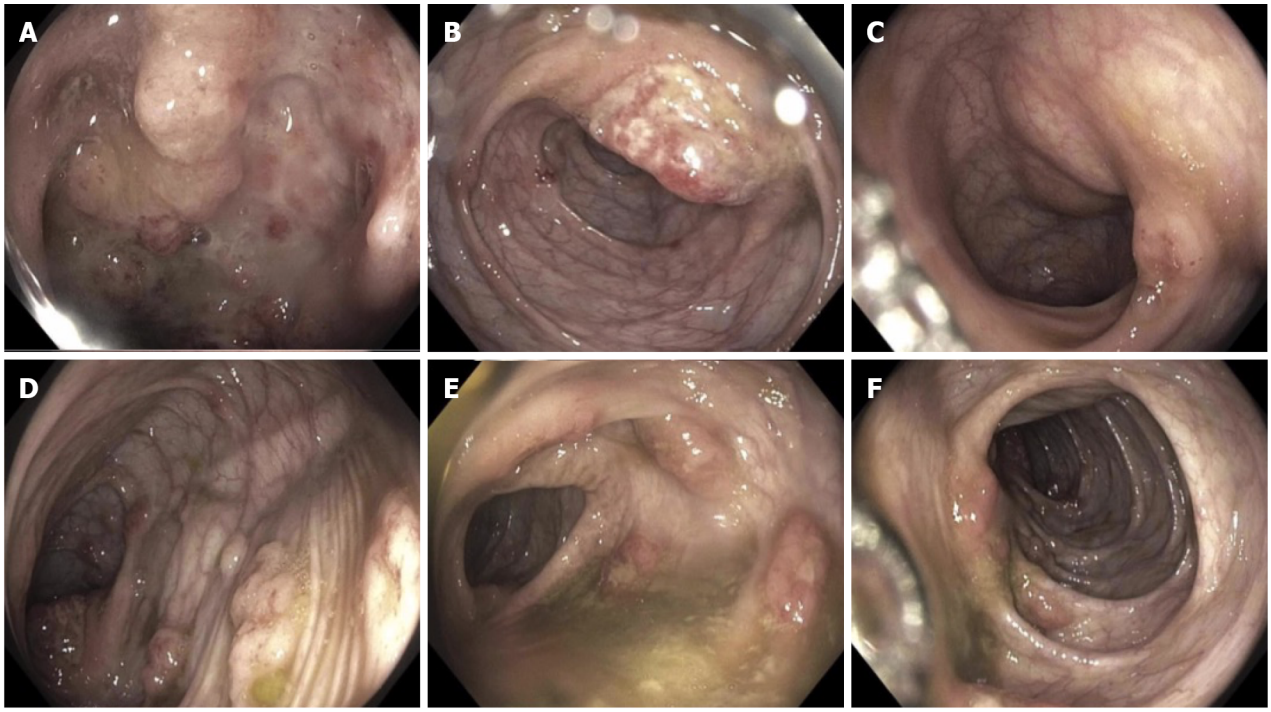

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Figure 1 Colonoscopy findings. Diffuse and severe inflammation characterized by mucosal edema, erythema, friability, pseudopolyps, and serpentine ulcerations. A: Terminal ileum; B: Ileocecal valve; C: Transverse colon; D and E: Descending colon; F: Ascending colon.

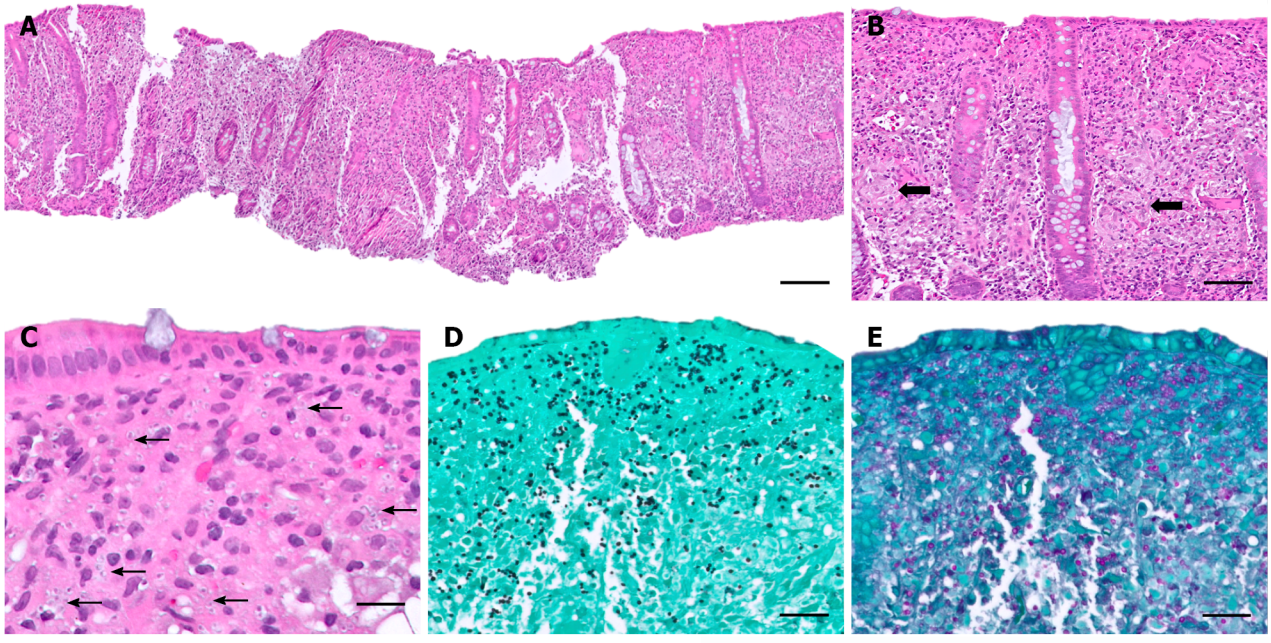

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Figure 2 Histologic findings. A: Colon biopsy revealed diffuse cellular infiltrate within the lamina propria (hematoxlyin and eosin, × 2, scale bar 1 mm); B: Scattered poorly formed granulomas (arrows) (hematoxlyin and eosin, × 20, scale bar 100 μm); C: Intracellular microorganisms (arrows) (hematoxlyin and eosin, × 40, scale bar 50 μm); Numerous yeast forms suggestive of *Histoplasma* spp. confirmed by special stains; D: Grocott-Gomori's Methenamine Silver stain (× 20, scale bar 100 μm); E: Periodic acid Schiff stain (× 20, scale bar 100 μm).

anti-*Histoplasma* antibodies further increases the sensitivity for diagnosis[12].

The terminal ileum is most commonly involved, presumably because of the lymphoid-rich tissue in this area, but can be found throughout the gastrointestinal tract[9]. The pathologic findings of gastrointestinal histoplasmosis include mucosal ulceration, polypoid lesions, and obstructing masses[6,11,13]. Histologically, tissue shows diffuse expansion of lamina propria and submucosa by macrophages containing intracellular yeast forms[6,10]. As in our case, due to similarities in presentation, pattern of

Table 1 Reports of histoplasmosis mimicking inflammatory bowel disease in pediatric immunocompetent patients: Cases published between 1970–present (including current case)

Ref.	No. of cases	Age/Sex	Clinical presentation	Initial concern	Immune status	Laboratory investigations
Soper *et al* [23], 1970	2	15/M	Periumbilical pain with radiation to back; prior exposure to *Coccidioides* and *Histoplasma*	Presumed CD	Immunocompetent	*Histoplasma* antibody titers 1:1024
		13/M	Abd pain, bilious vomiting, weight loss, fever; prior exposure to *Histoplasma*	Presumed CD	Immunocompetent	Not performed
Alberti-Flor and Granda [18], 1986	1	16/M	Abd pain, diarrhea, weakness, fever; history of Job syndrome	Presumed CD	Hyper-IgE syndrome	Complement fixation 1:64; yeast antigen 1:8; preciptin (H/M bands), GMS+ yeast forms (resection specimen)
Steiner *et al* [19], 2009	1	14/F	Fatigue, abd pain, fever, weight loss	Presumed CD	Hyper-IgE syndrome	Urine *Histoplasma* antigen (8.34 ng/mL), *Histoplasma* complement fixation titers 1:32 (mycelial phase) 1:64 (yeast phase), preciptin (H/M bands), Yeast forms (terminal ileum, ileocecal valve)
Agarwal *et al* [20], 2015	1	7/F	Intermittent fever and chills, weight loss	Presumed CD	Immunocompetent	Yeast forms (peripheral blood), GMS/PAS+ yeast forms (bone marrow)
Kweyamba *et al*[21], 2016	1	4/M	Intermittent vague abd pain, anorexia, occasional vomiting and nausea; obstructing mesenteric chylous cyst	Intestinal obstruction	Immunocompetent	PAS+ yeast forms (cyst lining)
Acharyya *et al* [22], 2021	1	8/M	Colicky abd pain, weight loss, constipation, subsequent ileal stricture	Presumed intestinal tuberculsosis, unresponsive to antitubercular medication × 9 mo	Immunocompetent	GMS+ yeast forms (ileum, mesenteric nodes)
Current case, 2022	1	12/M	Abdominal pain × several months, weight loss, bloody diarrhea	Presumed CD	Immunocompetent	GMS+ yeast forms (colon)

6-MP: 6-mercaptopurine; abd: Abdominal; CD: Crohn disease; GI: Gastrointestinal; IBD: Inflammatory bowel disease; NR: Not reported; UC: Ulcerative colitis.

involvement and associated granulomatous inflammation, gastrointestinal histoplasmosis can mimic CD[6,14-17].

To our knowledge, only 7 cases of isolated gastrointestinal histoplasmosis occurring in the pediatric age group (younger than 18 years of age) have been previously reported, mostly from individual case reports (Table 1)[18-22] and one small case series[23]. Ages ranged from 4 to 16 years with a median age of 13 years. Of the previously described cases, the male/female ratio was 5:2. Our patient presented at a slightly younger age than the median (12 years *vs* 13 years). The most common presenting symptoms included abdominal pain and weight loss, with diarrhea, anorexia, and fever appearing occasionally. Pulmonary symptoms at presentation or during the disease course were not reported in any case. Five patients were presumed immunocompetent[20-22], while two patients were known to have immunocompromising conditions (hyper-IgE syndrome) prior to their presentation[18,19]. One patient with hyper-IgE syndrome was effectively treated seven months prior for cough and fever of unknown origin [19]. As in our case, five patients were given a presumptive diagnosis of CD based on clinical presentation and endoscopic findings[20-23]. A broad range of diagnostic laboratory tests were performed including immunological tests for antigen and/or antibody detection. Microscopic examination revealed the presence of yeast forms (by routine hematoxylin and eosin staining and/or special staining methods) in all cases.

In our present case, the patient presented with gastrointestinal symptoms alone and endoscopic findings suggestive for CD and was started on corticosteroids and subsequently mesalamine. An interesting feature of our case is that while the gastrointestinal tract was the only site of symptomatic disease, it is unlikely to be the primary focus of infection. It is more likely that after inhalation of the fungus, dissemination by the bloodstream occurred before an immune response was mounted with some unidentifiable factor favoring persistence in the gastrointestinal tract exclusively. After additional workup, the patient was identified as more susceptible to histoplasmosis because of the dysregulation of cell-mediated immunity associated with his XHIGM and CVID, as suggested by his immunological

Table 2 Infectious mimics of inflammatory bowel disease[1]

Infectious etiology	Gastrointestinal site	Routine stain	Ancillary stain(s)
Bacterial			
E. coli, O157-H7[24]	Colon	H&E stain	Gram stain
Shigella spp.[25]	Colon		
Salmonella spp.[26]	Colon, terminal ileum		
Campylobacter spp.[27]	Colon, terminal ileum		
Yersinia enterocolitica[28]	Colon, terminal ileum		
Clostridiodes difficile[29]	Colon		
Nesisseria gonorrhoeae[30]	Colorectal		
Treponema pallidum[31]	Colorectal		
Chlamydia trachomatis[32]	Colorectal		
Aeromonas spp.[33]	Colon		
Mycobacterial tuberculosis[34]	Gastrointestinal tract, mostly terminal ileum		Gram stain Acid-fast stain (Ziehl-Neelsen or Kinyoun)
Fungal			
Cryptococcus spp.[35]	Terminal ileum	H&E stain	GMS stain
Histoplasma capsulatum[36]	Terminal ileum		PAS stain
Coccidioides spp.[37]	Colon		
Paracoccidioides spp.[38]	Colorectal		
Viral			
Cytomegalovirus[39]	Jejunoileal	H&E stain	CMV immunostain
Herpes simplex virus[40]	Colorectal		HSV I/II immunostain
Parasite			
Entamoeba histolytica[41]	Colon	H&E stain	Giemsa stain
Enterobius vermicularis[42]	Colorectal		Serology
Taenia saginata[43]	Ileum		Stool examination
Strongyloides stercoralis[44]	Colon		
Anisakis spp.[45]	Ileum		
Hookworm (*Ancylostoma duodenale, Necator americanus*)[46]	Jejunoileal		

[1]Adapted from Shojaei *et al*[47].
CMV: Cytomegalovirus; GMS: Grocott-Gomori's Methenamine Silver; H&E: Hematoxylin and eosin; HSV: Herpes simplex virus; PAS: Periodic acid-Schiff.

testing results. Distinction of these entities is vital as the optimal treatment for one disease could lead to exacerbation of the other. A list of infectious diseases that should be excluded in patients diagnosed as inflammatory bowel disease (IBD) is provided in Table 2.

CONCLUSION

Gastrointestinal involvement with *H. capsulatum* in the absence of pulmonary manifestations is exceedingly rare and may lead to delay in recognition due to overlapping symptoms with IBD. This case highlights the importance of excluding infectious etiologies in patients with "biopsy-proven" CD prior to initiating immunosuppressive therapies, especially in the setting of recent travel or exposure in an endemic area. Communication between clinicians and pathologists is crucial as tests for *Histoplasma*

antigen in urine or serum should be performed once histoplasmosis is suspected.

FOOTNOTES

Author contributions: Miller CQ served as the primary author; Miller CQ and Collins K are responsible for this literature review; Miller CQ, Saeed OAM, and Collins K were responsible in the construction of the manuscript; Collins K served as the senior author, provided invaluable educational input and managed the edits of the manuscript, and guided the primary author through the submission process; All authors read, revised, and gave approval of the manuscript.

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