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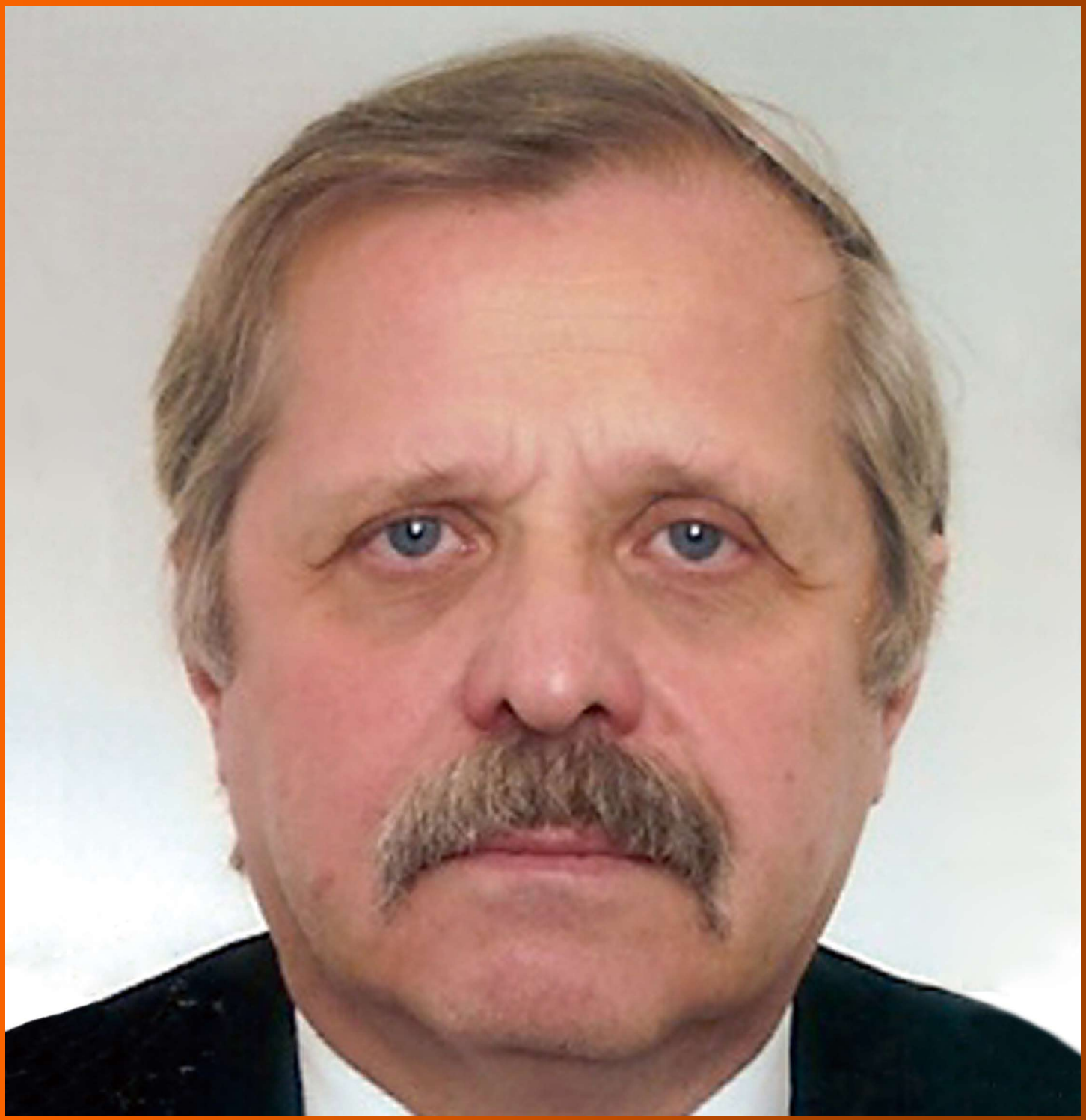

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RETROSPECTIVE STUDY

Increased postoperative complications after protective ileostomy closure delay: An institutional study

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Abstract

AIM: To study the morbidity and complications associated to ileostomy reversal in colorectal surgery patients, and if these are related to the time of closure.

METHODS: A retrospective analysis of 93 patients, who had undergone elective ileostomy closure between 2009 and 2013 was performed. Demographic, clinical and surgical variables were reviewed for analysis. All complications were recorded, and classified according to the Clavien-Dindo Classification. Statistical univariate and multivariate analysis was performed, setting a *P* value of 0.05 for significance.

RESULTS: The patients had a mean age of 60.3 years, 58% male. The main procedure for ileostomy creation was rectal cancer (56%), and 37% had received preoperative chemo-radiotherapy. The average delay from creation to closure of the ileostomy was 10.3 mo. Postoperative complications occurred in 40% of the patients, with 1% mortality. The most frequent were ileus (13%) and wound infection (13%). Pseudomembranous colitis appeared in 4%. Increased postoperative complications were associated with delay in ileostomy closure ($P = 0.041$). Male patients had more complications ($P = 0.042$), mainly wound infections ($P = 0.007$). Pseudomembranous colitis was also associated with the delay in ileostomy closure ($P = 0.003$). End-to-end intestinal anastomosis without resection was significantly associated with postoperative ileus ($P = 0.037$).

CONCLUSION: Although closure of a protective ileostomy is a fairly common surgical procedure, it has a high rate of complications, and this must be taken into account when the indication is made. The delay in stoma closure can increase the rate of complications in general, and specifically wound infections and colitis.

Key words: Protective ileostomy; Stomas; Stoma-related complications; Surgical infections; Colorectal surgery

Core tip: Protective ileostomies are widely used by surgeons for the protection of anastomoses, but they imply a second intervention for reversal. Despite being considered a minor intervention, ileostomy reversal does not lack complications. Adjuvant treatment, complications from the first intervention, or low-priority consideration can delay the closure of the stoma. In our study, we reviewed all complications following ileostomy reversal and found they were considerably high (40%), and increased as did the time (in months) until closure ($P = 0.041$). In multivariate analysis, male patients had more complications ($P = 0.042$), mainly wound infections ($P = 0.007$). Pseudomembranous colitis was also associated with the delay in ileostomy closure ($P = 0.003$).

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INTRODUCTION

Diverting loop ileostomies are widely used by colorectal surgeons for the protection of low rectal anastomoses, as they can reduce the morbidity and rate of reintervention if an anastomotic leak occurs[1]. The use of a protective ileostomy is specially indicated in very low rectal resections, coloanal anastomosis and pouches[2,3].

However, there can be an important morbidity associated to the stoma itself, deriving in a bad quality of life for the patient. Some common problems associated to the ileostomy can be electrolytic alterations, dehydration, renal failure, infection, obstruction, prolapse, and hernias[4]. Postoperative complications of variable severity (and even mortality) have been reported in different series reviewing protective ileostomy closure, ranging from 3% to over 40%[5,6]. Surgical infection of the wound is always a relevant one. A recent systematic review on ileostomy reversal reported an overall mortality of 0.4%[7], with values ranging from 0% to 4% in different studies. The aim of our study was to review our institutional series of ileostomy reversals and identify possible risk factors for postoperative complications.

MATERIALS AND METHODS

A retrospective analysis of patients who underwent elective ileostomy reversal in our institution between 2009 and 2013 (first semester) was performed. La Paz University Hospital (Madrid, Spain) is a tertiary care university hospital, with a high-volume Colorectal Surgery Unit. Ninety-three patients were included in the study. All data from the patients were retrieved from medical records and included in a database. Analyzed variables were: demographics, comorbidities, the American Society of Anesthesiologists classification for operative risk (ASA) index, body mass index (BMI), initial surgery (when the ileostomy was created), adjuvant chemo-radiotherapy before stoma closure, time interval from stoma creation to reversal, surgical technique employed, hospital stay, surgical complications, readmissions and mortality. All patients were assessed preoperatively by a member of the Colorectal Surgery Unit, who indicated the closure of the stoma, and by an Anesthesiologist for preoperative assessment. Regarding reversal, an oval incision was performed around the stoma to release the ileal loop. The anastomotic technique employed was either a handsewn end-to-end anastomosis without resection, a handsewn end-to-end with resection, a handsewn side-to-side with resection or a stapled anastomosis. Closure of the abdominal wall was performed with absorbable sutures (PDS or Vicryl©), and skin was closed with either staples, subcuticular or interrupted sutures, at surgeon's will. All these technical data were retrieved from the surgical charts and reports in the patients' records. Thirty-day morbidity and mortality were reviewed using medical records, outpatient clinic notes and the hospital's database.

Statistical analysis was performed using SPSS 16 Software for Windows, setting statistical significance at $P < 0.05$. χ^2 or Mann-Whitney tests were used for univariate analysis (when appropriate), and a multivariate analysis of all variables was performed.

Table 1 Characteristics of the 93 patients who underwent loop ileostomy reversal

Clinical characteristics	*n* (%)
Patients included, total	93 (100)
Gender	
Male	54 (58)
Female	39 (42)
BMI	
Underweight	3 (3.1)
Normal weight	44 (47)
Overweight	31 (33.3)
Obese	15 (15.8)
ASA Index	
I	5 (5.5)
II	59 (63)
III	29 (31)
Indication for ileostomy	
Colorectal cancer	52 (56)
Anastomotic leak	16 (17.2)
IBD	6 (6.4)
Colectomy for polyposis	5 (5.3)
Endometriosis	5 (5.3)
Diverticular disease	3 (3.2)
Intestinal necrosis	1 (1.07)
Pelvi-peritonectomy	1 (1.07)
Post-endoscopy perforation	1 (1.07)
Trauma	1 (1.07)
Adjuvant therapy (in oncological patients)	
Chemotherapy	16 (17.2)
Chemo-radiotherapy	35 (37)

Demographic data, BMI, ASA Index, indications for ileostomy creation and adjuvant therapy. BMI: Body mass index; ASA: The American Society of Anesthesiologists classification for operative risk; IBD: Inflammatory bowel disease.

RESULTS

The patients had a mean age of 60.3 years (range 22-88 years), 58% male. Demographic and clinical data, including the initial indication for ileostomy, are shown in Table 1. Data related to the interval from stoma creation to reversal, and the surgical technique employed for ileostomy and skin closure are shown in Table 2. A total of 26 patients (28%) presented at least one associated major comorbidity, including liver metastases (19%), diabetes and heart disease (11.5% each), pulmonary disease, thrombotic disease, hematologic disorders, lung metastases (7.7% each), and finally arrhythmias, other malignancies and tuberculosis (1% each). Average time for reversal was 10.3 mo, ranging from 1 to 36 mo. There was an 8.6% readmission rate due to dehydration before ileostomy closure. Postoperative complications globally occurred in 38 (40%) of the patients, and some patients presented more than one complication; these are detailed in Table

Table 2 Characteristics of the ileostomy reversal procedure, including surgical technique and skin closure

Surgical variable	*n* (%)
Ileostomy closure technique	93 (100)
Stapled anastomosis	9 (9.7)
Handsewn anastomosis	84 (90.3)
Side-to-side with resection	28 (33.3)
End-to-end with resection	8 (9.5)
End-to-end without resection	48 (57.1)
Skin closure technique	70 (100)
Staples	17 (24)
Subcuticular	29 (41)
Interrupted suture	24 (34)

Table 3 Postoperative complications after loop ileostomy reversal in our study

Complications	*n* (%)
Total patients	38 (40.8)
Ileus	12 (12.9)
Wound infection	12 (12.9)
Rectal bleeding	5 (5.8)
Pseudomembranous colitis	4 (4.3)
Anemia/bleeding	3 (3.2)
Intestinal obstruction	3 (3.2)
Anastomotic leak	2 (2.15)
Urinary tract infection	2 (2.15)
Acute renal failure	2 (2.15)
Abdominal abscess	2 (2.15)
Pneumonia	1 (1)
Intestinal necrosis	1 (1)
Multiple organ failure	1 (1)
Thromboembolism	1 (1)
Sepsis	1 (1)
Evisceration	1 (1)
Clavien-Dindo classification	
Grade Ⅰ	21 (55)
Grade Ⅱ	9 (24)
Grade Ⅲ	7 (18)
Grade Ⅳ	0 (0)
Grade Ⅴ	1 (3)

Total number of patients and detailed complications classified by the Clavien-Dindo classification.

Table 4 Statistically significant conditions/complications in the multivariate analysis and their specific *P* values

Condition/complication	Statistical significance
Gender (male) and overall complications	$P = 0.042$
Gender (male) and wound infection	$P = 0.007$
Age and rectal bleeding	$P = 0.006$
Complications and time to closure (months)	$P = 0.041$
Closure > 6 mo and pseudomembranous colitis	$P = 0.003$
End-to-end intestinal anastomosis (without resection) and postoperative ileus	$P = 0.037$

3. There was a 1% mortality. The mean hospital stay was 11.5 d, ranging from 3 d to 3 mo.

Multivariate analysis was performed to identify risk factors for complications. Male patients had complications in 50% of cases (27/54) while females did in 28% (11/39). This result reached statistical significance ($P = 0.042$), so in our study male sex was a risk factor for postoperative complications. When analyzing specific complications, there was a strong association between male sex and wound infection ($P = 0.007$). Age was associated to rectal bleeding ($P = 0.006$). There was no statistically significant association between complications and ASA, BMI, or previous chemo-radiotherapy.

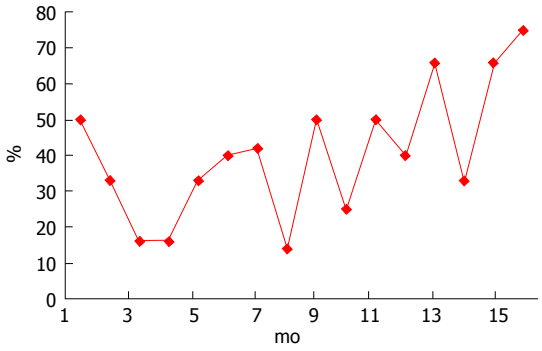

Figure 1 Percentage of postoperative complications related to ileostomy closure and time (in months) from creation to reversal.

In our series, the increased number of postoperative complications was associated with the delay in ileostomy closure ($P = 0.041$); a graphic representation of these data is shown in Figure 1. Occurrence of pseudomembranous colitis was also associated with the delay in ileostomy closure, with statistical significance ($P = 0.003$). The four cases of pseudomembranous colitis occurred in patients with ileostomy closure ranging from 9 to 15 mo.

According to the surgical technique for ileostomy reversal, only end-to-end intestinal anastomosis without resection was significantly associated with a specific complication, which was postoperative paralytic ileus ($P = 0.037$). There was no significant association between the surgical technique employed and postoperative hospitalization.

Regarding skin closure, the rate of surgical wound infection was studied in each group, when data on wound closure were available. In the staples group, infection was 5.8% (1/17 patients), in the subcuticular suture group 13% (4/29 patients) and in the interrupted suture group 20% (5/24 patients). Despite the rate of infection was highest in the interrupted suture group and lowest in the staples group these results did not reach statistical significance. All statistically significant results of the multivariate analysis are shown in Table 4.

DISCUSSION

Diverting loop ileostomies have become a common procedure when very low or high-risk rectal anastomoses are performed. Despite they can reduce morbidity and avoid reintervention if a leak occurs, their creation binds the patient to a second surgical procedure. This reversal procedure, as many published series have proven, can be associated to a high rate of morbidity, and even mortal-

ity[8]. In a recent systematic review[7], the high morbidity associated to ileostomy reversal raised concerns over the real indication of diverting stomas related to clinical outcomes, and if a better selection of patients should be made. Luglio *et al*[9], consider that if there is a > 5% risk of anastomotic leak in the primary operation, a protective stoma must be created.

In our study, the rate of postoperative morbidity was high (40%), but still among published data. The most common complications in our study were postoperative ileus and wound infections. Complications were mostly minor, classified as Clavien-Dindo Ⅰ-Ⅱ, and only 18% were considered major complications needing reoperation or invasive interventions (Clavien-Dindo Ⅲ). In a national study by Mengual-Ballester *et al*[6] data were similar to our own, with complications up to 45.9%, being ileus/obstruction the most frequent, followed by diarrhea and wound infection.

Ileus and bowel obstruction are still a concern after stoma reversal, and different studies have tried to elucidate if technical issues can reduce these complications. The surgical technique employed for the ileal anastomosis has been widely studied, and various published randomized controlled trials (RCTs) compare handsewn *vs* stapled anastomoses[10,11]. In our study, when analyzing the surgical technique and related complications, we only found statistical significance between end-to-end anastomosis without resection and postoperative paralytic ileus. This coincides with published meta-analysis[12-14] which mention a significant reduction in surgical time and a lower incidence of bowel obstruction when stapled anastomoses are performed compared to handsewn. Other complications (including infections, leak, readmission and reoperation rates) are similar.

Surgical infections after stoma reversal have been a subject of debate. Although both ileostomies and colostomies can be safe, the latter present a higher rate of infection after reversal. Therefore many authors recommend protective ileostomies for fecal diversion, if dehydration is not to be expected[15]. The rate of wound infection in our study (12.9%) was similar to other published data[16]. Wound infection is usually underestimated due to different definitions or considerations, and can be influenced by patient's characteristics and comorbidities. In some series of ileostomy closure for pouch-anal anastomoses such as that from van Westreenen *et al*[3], only a 1.4% rate of infection is reported. When analyzing patient's characteristics we realize mean age is only 49 years, most patients are ASA Ⅰ-Ⅱ, and indications for ileostomy are polyposis or inflammatory bowel disease rather than cancer. Data are therefore not comparable if the population of study is older or weaker. In our series, mean age was 60 years and patients mainly ASA Ⅱ-Ⅲ, with the main indication for ileostomy creation being colorectal cancer (56%).

Another important factor is if the 30-d infection rate is reported, or just the rate of infection during hospitalization. This can underestimate infections, as many of them occur after discharge and are managed in the outpatient clinic or by General Practitioners. This has been taken into consideration, and some recent publications already study standardized 30-d complications[17], and use classifications such as Clavien-Dindo to report results[9].

Different efforts have been made to reduce the infection rate of stoma-closure wounds. The technique employed has shown statistically significant results in various RCTs, such as that from Camacho-Mauries *et al*[18], favoring purse-string closure *vs* conventional sutures. In our study, a limitation regarding the retrospective analysis of skin closure was that data were incomplete and some surgical reports did not state the specific closure technique. From those available, interrupted, non absorbable sutures were the most frequently used, followed by subcuticular and staples. The staples group had a lower infection rate, but these data were not significant. Studies on the subject show contradictory results. In the retrospective study by Kobayashi *et al*[19], wound infection rate was as high as 23.5%, and subcuticular sutures apparently showed a protective effect. However, very recent studies and RCTs on wound closure, report purse-string sutures to achieve a 0% infection rate compared to other methods, thus not recommending linear closure of stoma wounds[20,21]. Other attempts, such as subcutaneous antibiotic implants (Gentamycin) in the wound, have not shown a relevant reduction in surgical site infections[22].

Another controversy around the subject is the best timing for stoma reversal. Some groups defend very early closure, even during the first admission, such as Alves *et al*[23], who perform reversal on the 8th postoperative day if no complications of the first intervention have occurred. Nevertheless, it is widely accepted to delay closure, and different studies report mean times of 3-6 mo, with a low medical priority given to this procedure[24].

In our study, we demonstrate that the delay in ileostomy closure (> 6 mo) is a risk factor for increased complications, and is associated with a higher incidence of pseudomembranous colitis, which was 4.3%. As can be seen in Figure 1, the incidence of complications increased with time (in months); there was an apparently 'safer' period around 3-6 mo, which could be considered optimal. From 9 mo onwards the rate of complications was > 30%.

Pseudomembranous colitis (PMC) is secondary to *Clostridium difficile* (*C.diff*) infection, and associated with substantial morbidity and mortality, increased duration of hospitalization, and a marked economic impact[25]. *C.diff* is a toxin-producing anaerobic bacterium responsible for antibiotic-associated colitis, and it is now the most common infectious cause of nosocomial diarrhea. Risk factors for PMC include advanced age, systemic antibiotic therapy, hospitalization, nursing homes or long-term care facilities, contact with active carriers, and presence of comorbidities[26]. It has been speculated that stoma closure can be another risk factor for PMC, which associates all the previous to an excluded and defunctioned bowel with altered flora, that could be more susceptible to *C.diff*

infection[27]. In a large series of 13245 United States patients undergoing ileostomy closure, Wilson *et al*[28], report a 1.6% incidence of pseudomembranous colitis. This is an important factor to be considered, especially if an earlier closure can in fact reduce the risk.

This study was a retrospective analysis of institutional patients in order to identify risk factors for postoperative complications after ileostomy reversal and improve quality of care in our Colorectal Surgery Unit. Therefore, limitations are all those of an observational retrospective study, and in some cases (as in skin closure technique) data were missing from medical records. Due to the small number of patients some data may not reach statistical significance.

Although closure of a protective ileostomy is a fairly common surgical procedure, it has a high rate of complications, and this must be taken into account when the indication is made. The delay in stoma closure can increase the rate of complications in general, and specifically wound infections and colitis.

COMMENTS

Background

The creation of a defunctioning stoma after some colorectal procedures has demonstrated to highly reduce morbidity and mortality rates if a leak occurs, and is usually widely recommended. However, a stoma can be an issue for many patients both psychologically and due of stoma-related complications. As these stomas are supposed to be temporary, a planned second operation for reversal must be performed. In some cases, due to cancer-related complications or comorbidities stomas are never reversed. In patients considered fit for surgery, the reversal of the stoma should be performed at the "safest" time possible, to reduce complications. This timing is sometimes difficult to determine, as it depends on clinical factors, oncological follow-up and treatment, surgeon's decision and institutional issues, such as "low-priority" consideration in surgical waiting lists.

Research frontiers

In the field of Colorectal Surgery, the optimization of anastomoses and methods to reinforce or protect them to avoid leaks is a matter of active research. Eventually, the creation of stomas would become obsolete if this could be achieved, improving surgical outcomes and reducing complications.

Innovations and breakthroughs

When revising the literature for the optimal timing for stoma reversal, recommendations usually suggest a 3 to 6 mo interval after the first intervention, always tailored to the specific risk factors and situation of the patient. When revising the real timing in our general practice, the authors realize there is a significant delay, and these recommendations are not followed. Complications related to prolonged bowel defunctioning (such as ileus, bleeding, diarrhea or *Clostridium difficile* colitis) and wound infections could be reduced if the time for closure is optimal. The best practice would be to guarantee an adequate healing from the first operation and close the stoma early enough to avoid the consequences of a prolonged defunctioning.

Applications

The study suggests that there is an optimal time frame to be considered when planning the ileostomy reversal that could reduce postoperative complications.

Terminology

A protective ileostomy is an opening of a loop of small bowel (usually the terminal ileum) in the abdominal wall, so that a distal anastomosis performed in the colon or rectum is protected from fecal matter and can heal properly. The ileostomy reversal is the surgical intervention performed to close the loop of small bowel and restore normal intestinal transit.

Peer review

Abstract is concise, topic is interesting, methods are appropriate, a well-structured discussion.

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Pancreatic extragastrointestinal stromal tumor: A case report and comprehensive literature review

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Abstract

AIM: To provide an overview of the literature on pancreatic extragastrointestinal stromal tumors (EGISTs).

METHODS: We report a case of pancreatic EGIST and review published studies on pancreatic EGIST accessed *via* the PubMed, MEDLINE, Google Scholar, and Google databases. The keywords used were "pancreas and GIST", "pancreas and extra GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor". Literature reviews and/or duplicate studies were excluded. The search included articles published in the English language between January 1, 2000 and May 15, 2014.

RESULTS: From our literature survey, 30 manuscripts on pancreatic EGISTs were considered, of which 27 met the search criteria and three were excluded. The studies involved 30 patients (15 men, 15 women) with a mean age of 55.3 ± 14.3 years (range 30-84 years). The mean age of the male patients was 50.8 ± 13.7 years (range 30-84 years); that of the female patients was 59.9 ± 13.3 years (range 38-81 years). Tumor dimensions were obtained for 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). Tumors were diagnosed incidentally in 23.3% of patients; abdominal discomfort and weight loss were the major complaints in symptomatic patients. Risk of aggressive behavior according to Fletcher criteria was determined in 25 of 30 patients (68%: high risk, 28%: intermediate risk, 4%: low risk). Histopathological examination revealed the presence of spindle cells in 96.1% of cases; CD117 and CD34 were present immunohistochemically in 96.6% and 84% of patients, respectively. The most common surgical procedures were distal pancreatectomy with splenectomy (n = 9) and pancreaticoduodenectomy (n = 7). The total follow-up period for the 28 patients ranged from 3-66 mo, during which locoregional or distant metastases were diagnosed in six patients and two patients died.

CONCLUSION: Studies on EGISTs have only been published in the last decade. The lack of studies with large patient cohorts and long-term follow-up limits evidence-based commentary. In theory, each case should be assessed individually and further genetic and immunohistochemical studies are needed.

Key words: Gastrointestinal stromal tumor; Extra-gastrointestinal stromal tumor; Pancreas; Imatinib mesylate; CD117

Core tip: Gastrointestinal stromal tumors are the most common gastrointestinal (GI) tract tumors of mesenchymal origin. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI

tubular organs or the serosal walls. The pancreas is among the organs that are rarely the site of origin, and according our knowledge, about 30 cases of pancreatic EGISTs have been reported to date. In this study, we reviewed studies on pancreatic EGISTs and report a case of pancreatic head EGIST.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract[1-3]. The disease originates from neoplastic transformation of the interstitial cells of Cajal or their precursors in the GI tract. Although GISTs can be diagnosed in all sites of the GI tract, *i.e.*, from the esophagus to the anus, they are most commonly diagnosed in the stomach and intestines[1-6]. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces[3,7,8]. The morphological, histopathological, immunohistochemical, and molecular profiles of EGISTs are similar to those of GISTs[2,9,10]. Although EGISTS potentially originate from a variety of sites in the abdominal cavity, the majority of initial tumor progression sites include the omentum, retroperitoneum, mesentery, and the liver[1,2,11,12]. The pancreas is rarely the site of origin, and according our knowledge, 30 cases of pancreatic EGISTs have been reported to date[1-5,7-31]. We report a case of pancreatic EGIST and review the literature on pancreatic EGISTs.

MATERIALS AND METHODS

Our primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. We searched for published studies on pancreatic GIST using different keyword combinations, including "pancreas and GIST", "pancreas and extra-GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor" in the PubMed, MEDLINE, Google Scholar, and Google databases. Studies for which full-text versions were available and that contained adequate patient details for comparison were included; literature reviews and duplicate reports were excluded. The publication language was not an exclusion criterion, and studies published before May 15, 2014 were included. Tables 1 and 2 lists the year of publication, country, patient age and sex, clinical presentation, physical examination, radiological tests, tumor size (mm), cell type (spindle, epithelioid, mixed), mitotic count [per high-power field (HPF)], immunohistochemical staining (CD117, CD34), surgical procedure, recurrence, outcome, and follow-up obtained from the studies.

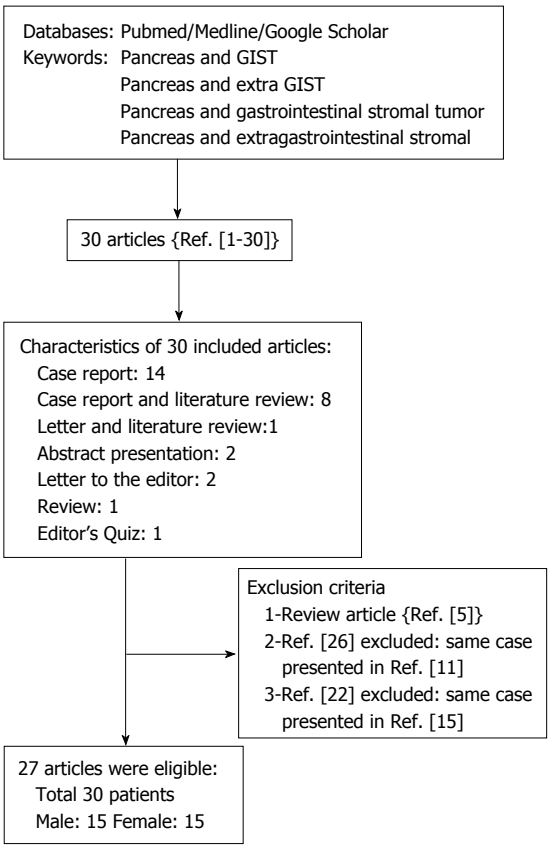

Figure 1 Flow chart of the study selection process. GIST: Gastrointestinal stromal tumor.

RESULTS

Literature review

Based on the above-mentioned search criteria, 30 manuscripts were identified[1-5,7-31]: 27 met the criteria and three were excluded[5,22,26]. The criteria are detailed in the flow chart in Figure 1. The studies involved 30 patients with pancreatic GIST: 15 were male and 15 were female; mean age was 55 ± 14.3 years (range 30-84 years). The mean ages of male and female patients were 50.8 ± 13.7 years (range 38-81 years) and 59.9 ± 13.3 years (range 38-81 years), respectively. Information regarding tumor size was obtained from 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). The demographic and clinical data of the 30 patients are presented in Table 1. Table 2 summarizes the morphological characteristics, treatments, and outcomes of the 30 patients.

Case report

A 61-year-old woman was admitted to our clinic for a routine check-up. One year previously, she had visited another clinic complaining of loss of appetite, weight loss,

Table 1 Demographic and clinical characteristics of 30 patients with pancreatic extragastrointestinal stromal tumors identified from literature published between January 2004 and May 2014

Ref.	Year	Country	Age (yr)	Sex	Clinical presentation	Examination	Radiologic tools	Tumor location	Tumor size (cm)
Tian *et al*[4]	2014	China	61	M	Incidental finding	Abdominal mass	CT	Tail	60 × 80
			60	M	Incidental finding	NS	CT	Head	60 × 50
Paklina *et al*[11]	2013	Russia	38	F	Abdominal discomfort	NS	CT	Head	90
Serin *et al*[1]	2013	Turkey	30	M	Abdominal distension	NS	US + CT	Tail	130
Soufi *et al*[16]	2013	Morocco	39	M	Weight loss + abd pain + constipation	Distension	CT + endoscopy	Head	90 × 70 × 50
Wegge *et al*[2]	2012	USA	55	M	Haematemesis + haematochezia	Non-specific	CT + MRCP + endoscopy	Head	46 × 45 × 44
Babu *et al*[13]	2012	China	55	F	Upper abdominal pain	Non-specific	CT + US	Head	50 × 40 × 30
Kim *et al*[3]	2012	Korea	55	M	Abdominal discomfort	Non-specific	CT + MR	Tail	130 × 90 × 85
Čečka *et al*[9]	2011	Czech	74	F	Abdominal mass	Palpable mass	US + CT	Tail	110 × 80 × 40
Vij *et al*[14]	2011	India	35	M	Weight loss + abdominal discomfort	Non-specific	US + CT	Head	80 × 60
Rao *et al*[7]	2011	India	40	M	Weight loss + abdominal pain + anemia	Non-specific	US + CT	Head + Body	65 × 60
Yang *et al*[15]	2011	China	55	M	Abdominal discomfort	Abdominal mass	CT + MR	Body + Tail	178 × 196
Barros *et al*[12]	2011	Brasil	63	F	Abdominal pain + ponderal loss	NS	NS	NS	NS
			81	F	Difficult gastric emptying + ponderal loss	NS	NS	NS	100
Joshi *et al*[17]	2010	USA	84	M	Weight loss + abdominal distension	Distension	CT	Entire pancreatic tissue	340 × 240 × 270
Crisan *et al*[18]	2010	Romania	61	M	Weight loss + fever + intense sweating	Diffuse tenderness	CT X	Tail + Body	140
Saif *et al*[19]	2010	USA	31	M	Weight loss + abdominal pain + anemia	NS	CT + MR + endoscopy	Head	56 × 51 × 42
Padhi *et al*[8]	2010	India	42	F	Weight loss + abdominal pain	Palpable mass	CT + MR	Body + Tail	350 × 300 × 250
Harindhanavudhi *et al*[20]	2009	USA	63	F	Fatigue + weakness+anemia	Non-specific	CT + EUS	Body	160 × 110
Trabelsi *et al*[21]	2009	Tunisia	52	F	Epigastric pain	Palpable mass	US + CT	Head	105 × 80 × 30
Goh *et al*[10]	2009	Singapore	58	M	Incidental finding	NS	NS	Head	90
Showalter *et al*[23]	2008	USA	72	F	Incidental finding	NA	MR	Tail	70
Yan *et al*[24]	2008	USA	47	M	Nausea + vomiting + (hepatitis B)	Splenomegaly	CT + EUS	Uncinate process	24 × 21
Ganesh *et al*[25]	2008	UK	76	F	Weight loss + abdominal pain	Diffuse tenderness	CT + endoscopy	Tail + body	NS
Daum *et al*[27]	2005	Czech	70	F	Incidental finding	Palpable mass	CT	Head	100 × 80 × 60
Krska *et al*[28]	2005	Czech	38	F	Abdominal pain + fatigue	Tenderness	CT + US + EUS + CT + endoscopy	Head + Body	170 × 120
Pauser *et al*[29]	2005	USA	51	M	Incidental finding	NS	US + CT + endoscopy	Tail	30
			54	F	Abdominal discomfort	NS	US	Body	20
Neto *et al*[30]	2004	Brasil	67	F	Weight loss + abd pain + gastric bloating	NS	NS	Body + Tail	200 × 190 × 120
Yamaura *et al*[31]	2004	Japan	54	F	Incidental finding	Palpable mass	US + CT + MR + angiography	Tail	140 × 120 × 80

US: Ultasonography; CT: Computed tomography; MR: Magnetic resonance; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; X: Partial thrombosis detected in both portal vein and inferior vena cava at the level of left renal vein; NA: Not-available; NS: Not-stated; M: Male; F: Female; UK: United Kingdom; USA: United States of America.

and jaundice. Blood tests showed elevated liver enzymes and leucocyte count. Abdominal ultrasonography (USG) revealed bile duct dilatation, multiple metastatic liver lesions, and a pancreatic head mass. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 97 mm × 63 mm heterogeneous mass with well-defined margins in the pancreatic head, which had resulted in the bile duct dilatation. Perihilar gross lymphadenopathy was also detected. Following bile duct decompression by percutaneous transhepatic cholangiography, percutaneous biopsy samples were collected from the liver lesions and portal lymph nodes under USG guidance. The specimens were evaluated histopathologically and immunohistochemically [CD117(+); CD34(−); smooth muscle actin (SMA)(−)], and GIST was diagnosed. As the primary tumor was metastatic prior to surgery, 400 mg/d imatinib mesylate (Gleveec®, Novartis) was started and administered for four months. MRI subsequently showed a reduction in tumor size to 15 × 15 mm. CT performed during the same period showed that the tumor had shrunk to 15 × 20 mm and that the liver lesions had disappeared. Based on these findings, surgical treatment was advised, but the patient refused surgery; therefore, she was discharged and prescribed imatinib. When admitted to our clinic, she had no significant physical findings except

Table 2 Morphological characteristics, treatments, and outcomes of 30 patients with pancreatic extragastrointestinal stromal tumor identified from literature published between January 2004 and May 2014

Ref.	Cell type	Mitotic count (/50 HPF)	CD117	CD34	Surgical procedures	Recurrence (after surgery)	Outcome (follow-up)	Medical treatment
Tian *et al*[4]	Spindle	< 5 (intermediate risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (36 mo)	No
	Spindle	> 5 (high risk)	(+)	NS	Tumor resection	Yes (liver, 12 mo)	Alive (36 mo)	Gleevec + TACE
Paklina *et al*[11]	Spindle	1-2 (intermediate risk)	(+)	NS	NS	NS	NS	NS
Serin *et al*[1]	NS	NS (high risk)	(+)	NS	Distal pancreatectomy + splenectomy	No	Alive (21 mo)	No
Soufi *et al*[16]	Spindle	< 5 (intermediate risk)	(+)	(+)	Whipple + segmental colectomy	No	Alive (24 mo)	Gleevec
Wegge *et al*[2]	Spindle	6 (intermediate risk)	(+)	(+)	Whipple	No	Alive (5 mo)	Gleevec
Babu *et al*[13]	Spindle	6-8 (high risk)	(+)	(+)	Pancreatic head resection	No	Alive (11 mo)	No
Kim *et al*[3]	Spindle	7 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (4 mo)	Gleevec
Čečka *et al*[9]	Spindle	5 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (66 mo)	No
Vij *et al*[14]	Spindle	12-15 (high risk)	(+)	(-)	Whipple	Yes (liver, 24 mo)[a]	Alive (48 mo)	Gleevec
Rao *et al*[7]	Spindle[b]	8-10 (high risk)	(+)	(+)	Whipple	Yes (liver, 24 mo)	Alive (30 mo)	Gleevec
Yang *et al*[15]	Spindle	> 30/10 HPF (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	Yes (intraperitoneal, 24 mo)[c]	Alive (41 mo)	Gleevec
Barros *et al*[12]	NS	< 5	(+)	(+)	No	NS	Death (8 mo)	No
	NS	< 5 (intermediate risk)	(+)	(+)	Laparotomy + biopsy	Surgery not performed	Alive (12 mo)	Gleevec
Joshi *et al*[17]	Spindle	NS	(+)	(+)	None performed[d]	Surgery not performed	Death (5 d)	No
Crisan *et al*[18]	Spindle	(high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial colectomy + duodenojejunal resection	NS	Alive (3 mo)	NS
Saif *et al*[19]	Spindle[e]	48 (high risk)	(+)	(-)	Whipple, pylorus preserving	Yes (liver, 9 mo)	Alive (NS)	Gleevec
Padhi *et al*[8]	Spindle	6-8 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + left hemicolectomy	No	Alive (10 mo)	No
Harindhanavudhi *et al*[20]	Spindle	< 5 (high risk)	(+)	(+)	Cystojejunostomy[f]	NS	Alive (NS)	Gleevec
Trabelsi *et al*[21]	Spindle	6 (high risk)	(+)	(+)	Whipple + partial colectomy	No	Alive (10 mo)	No
Goh *et al*[10]	Spindle	> 10 (high risk)	(+)	NS	Whipple	No	Alive (58 mo)	NS
Showalter *et al*[23]	NA	3 (intermediate risk)	(+)	(-)	Distal pancreatectomy + splenectomy - laparoscopic	No	Alive (27 mo)	NS
Yan *et al*[24]	Spindle[g]	3 (low risk)	(+)	NS	NS	NS	NS	NS
Ganesh *et al*[25]	Spindle[h]	NS	(+)	(+)	No (inoperable)	Surgery no performed	Alive (30 mo)	Gleevec
Daum *et al*[27]	Spindle	2 (intermediate risk)	(+)	(-)	Whipple	No	Alive (6 mo)	Gleevec
Krska *et al*[28]	Spindle[i]	1 (high risk)	(-)	(+)	Partial pancreatectomy	No	Alive (30 mo)	NS
Pauser *et al*[29]	Spindle	NS	(+)	(+)	Resection	No	Alive (24 mo)	NS
	Spindle	NS	(+)	(+)	Resection	No	Alive (48 mo)	NS
Neto *et al*[30]	Mixed	120 (high risk)	(+)	(+)	Distal pancreatectomy	Yes (peritoneum)	Alive (NS)	Gleevec
Yamaura *et al*[31]	Spindle	Few (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial gastric resection	NS	Alive (30 mo)	NS

[a]Liver metastasis at postoperative month 24. Metastasectomy performed. Two years followed without recurrence; [b]Diagnosed using USG-guided fine needle aspiration (FNA); [c]Intraperitoneal recurrence at postoperative month 24. Resection performed. Imatinib treatment both before and after resection. Following second resection, followed-up without recurrence; [d]CT-guided liver biopsy diagnosed metastatic EGIST. Clinical status deteriorated prior to surgery and died five days following diagnosis; [e]Diagnosed with Endo-USG (EUS)-guided FNA. Liver lesion diagnosed with CT and PET at postoperative month 9. Biopsy diagnosis was EGIST. Gleevec treatment dose increased to 800 mg. Due to resistance to treatment, was switched to sunitinib; [f]Pancreatic mass diagnosed four years ago, patient refused surgical treatment. CT revealed 10-cm enlargement in four years. Diagnosis was made with EUS-guided FNA. Explorative laparotomy revealed pancreatic hemorrhagic cyst; cystojejunostomy performed to obtain an incisional biopsy sample diagnosed high-risk GIST. Patient refused definitive surgical treatment; [g]Diagnosis made with EUS-guided FNA; [h]Diagnosed using USG-guided FNA. Further surgical treatment aborted as the patient was inoperable, and Gleevec treatment was initiated. Clinical follow-up period of 30 mo revealed significant tumor reduction; [i]USG-guided biopsy could not provide diagnosis. CT: Computed tomography; USG: Ultrasonography; EGIST: Extragastrointestinal stromal tumor; PET: Positron emission tomography; TACE: Transcatheter arterial chemoembolization; NA: Not-available; NS: Not-stated.

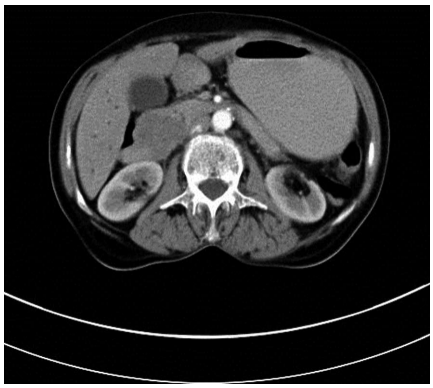

Figure 2 Contrast-enhanced abdominal computed tomography shows a well-defined solid mass of the pancreatic head.

cachexia. Laboratory test parameters, including tumor markers, were within the normal limits. Control abdominal CT scan showed that the tumor measured 45 mm × 40 mm (Figure 2). The common bile duct and major pancreatic duct diameter was 17 mm and 7 mm, respectively. No metastatic liver lesions were detected. F-18 fluorodeoxyglucose positron emission tomography-CT (PET-CT) detected a mass with increased glucose consumption at the duodenal site, consistent with a malignant lesion. Given the increased tumor size and the current complaints of the patient, surgical treatment was recommended. We detected a well-demarcated, 50 × 40 mm, semi-solid, visually heterogeneous pancreatic head mass without invasion to the surrounding tissues. Metastatic liver lesions were not observed, and lymphadenopathy was detected in the peripancreatic site and hepatoduodenal ligament. Standard pancreaticoduodenectomy with lymph node dissection was performed. The postoperative course was uneventful; she was discharged on day 13. Pathologically, the specimen contained tumor cells with low mitotic activity, severe pleomorphism, and cellularity (spindle cells); we diagnosed GIST. Postoperative imatinib mesylate was started, and there was neither locoregional nor distant metastases at the last follow-up 48 mo later.

DISCUSSION

In 1892, Cajal first observed interstitial cells of Cajal in the intestinal wall under a light microscope, which were termed "interstitial neural cells". Approximately 80 years later, Faussone-Pellegrini *et al*[32] viewed the same cells under an electron microscope and renamed them interstitial cells of Cajal[5,32]. Studies conducted during the 1970s showed that pathological changes to interstitial cells of Cajal may result in GI motility disorders and GISTs[5]. Since they were first described histologically, physiological testing has proven that interstitial cells of Cajal function as GI pacemakers[5,20,32,33].

Defined by Mazur and Clark in 1983, GISTs are the most common non-epithelial mesenchymal tumors of the GI tract[5]. Genetic studies have revealed that 90% and 5%-7% of GISTs have tyrosine kinase gene mutations in c-KIT and platelet-derived growth factor receptor alpha (PDGFRA), respectively[1,5]. The incidence of GIST varies between 10 and 20 cases per million people annually[5,9]. GISTs represent 0.1%-3% of all GI tumors and 80% of GI mesenchymal tumors, and may present at any site in the GI tract where there are interstitial cells of Cajal. The most frequently affected GI organs are the stomach (40%-70%), intestines (20%-40%), rectum and colon (< 10%), and the esophagus (rare)[5].

"EGIST" was initially used by Reith *et al*[33] in 2000 to define stromal tumors originating from outside the GI tract. EGISTs represent 5%-10% of all GISTs[1,4,5,9,12]. Although the locations from which EGISTs originate do not contain interstitial cells of Cajal, cells with the same clinical, pathological, immunohistochemical, transmission electron microscopy morphology, and biological behavior patterns as interstitial cells of Cajal have been detected[2,5,6]. Experimental and clinical studies have detected cells with biological and histopathological features similar to interstitial cells of Cajal in pancreatic tissue (interstitial Cajal-like cells = telocytes)[5,34]. The pancreas and GI tubular organs have a common embryological origin, suggesting that EGIST and GIST cells originate from multipotent mesenchymal stem cells (intestinal mesenchymal precursors)[1,5,21]. Several EGIST studies have suggested that most EGISTs are likely mural GISTs with diffuse extramural invasion resulting in loss of communication with the intestinal muscularis propria. This may occur during operative or postoperative manipulation. Furthermore, true EGISTs may be extramurally growing GISTs that lose communication with the muscularis propria after reaching this layer[2,10,16]. This is known as extensive extramural growth and requires further study.

More than 80% of EGISTs originate from EGI abdominal wall structures, including the intestinal mesentery, mesocolon, omentum, retroperitoneum, abdominal wall, liver, and pancreas[10,13]. Pancreatic EGISTs represent less than 1% of malignant pancreatic tumors, and less than 5% of EGISTs originate from the pancreas[16].

The majority of EGISTs are well demarcated and unencapsulated. Due to their slow growth rate, they may exist without any clinical signs until the majority of the abdominal cavity is invaded. Among the reported cases, tumors are 100-120 mm in diameter (range 10-400 mm)[4]. EGISTs are usually diagnosed in adults, predominantly in females[14]. Our literature review determined near equal rates of occurrence between females and males.

Pancreatic EGISTs are usually asymptomatic or minimally symptomatic and diagnosed incidentally by radiological examination[7,9]. When present, the severity of symptoms is related to tumor dimensions and location in the pancreatic tissue[2,4,7,9,16]. The most common symptoms and findings are nonspecific abdominal pain, weight loss, fatigue, abdominal mass and distention, fever of unknown origin, obstruction, GI bleeding, anemia, portal vein thrombosis, jaundice, and hepatic encephalopathy (rare)[4,16,18]. Of the cases we reviewed, 23.3% were diagnosed incidentally. The most common symptoms were

weight loss and abdominal discomfort.

The most common diagnostic studies for pancreatic masses involve biochemical [carbohydrate antigen 19-9, carcinoembryonic antigen (CEA)], radiological, histopathological, immunohistochemical, and genetic testing[3-5,21]. However, the diagnostic value of tumor markers such as CA 19-9 and CEA for pancreatic EGIST is limited, and are rarely used[4]. Abdominal CT, MRI, USG, endoscopic USG (Endo-USG), and PET-CT are the most frequently used radiological techniques, and aid in determining tumor localization, dimensions, margin irregularity, invasion of surrounding tissues, distant metastases, and resectability; however, most of them are non-diagnostic. USG and CT are often used in fine needle biopsies[5,7,17,20,24,25,28]. Endo-USG is a valuable diagnostic tool, allowing simultaneous diagnosis and biopsy of solid or cystic pancreatic masses[4,5,16,19,20,24]. PET-CT is used more frequently for both diagnosing and monitoring GIST and is very efficient in cases where CT and MRI are inconclusive[35].

Histopathologically, GISTs are classified into spindle (70%), epithelioid (20%), or mixed (< 10%) type. Most pancreatic EGISTs consist of spindle cells[4]. Therefore, leiomyoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, schwannoma, fibromatosis, inflammatory fibroid polyps, solitary fibrous tumor, and malignant fibrous histiocytoma should be considered in the differential diagnoses[3,8,11,24,27]. Of the cases presented here, 26 had detailed histopathological data and 25 (96.1%) had spindle cells.

EGISTs have typical immunohistological staining features, among which CD117 is the most well known. KIT is a transmembrane receptor for binding tyrosine kinase enzymes, and c-KIT is a newly discovered member of this receptor family, on whose receptor CD117 is an epitope that can be stained immunohistochemically. The introduction of CD117 staining in the 1990s changed the terminology for connective tissue tumors; since then, 95% of tumors defined as GIST or EGIST stain CD117-positive. For the 5% of tumors with negative staining, another tyrosine kinase receptor family member, PDGFRA, was investigated in immunohistochemical studies, with 33.3% positive staining[5]. Additionally, GISTs stain positive for CD34 (60%-70%), heavy caldesmon (80%), SMA (30%-40%), S100 (5%), and desmin (< 5%)[2-4,8,9]. Of the 30 cases presented, 29 (96.6%) stained CD117-positive and 21 (84%) of 25 cases stained CD34-positive.

Predicting GIST clinical and biological behavior is difficult. Fletcher defined the criteria of the National Institutes of Health (Fletcher criteria) to estimate the risks of GIST aggressive behavior and metastasis (locoregional and/or distant) using tumor dimensions (cm) and mitotic counts (per 50 HPF)[2,9]. According to the criteria, GISTs are classified based on their risk of aggressive behavior: very low (< 2 cm, < 5/50 HPF), low (2-5 cm, < 5/50 HPF), intermediate (< 5 cm, 6-10/50 HPF or 5-10 cm, < 5/50 HPF), and high (> 5 cm, > 5/50 HPF or > 10 cm, any mitotic count)[3,4,9,21]. This classification aids in surgical treatment selection or neoadjuvant and/or adjuvant treatment planning. The risk of aggressive behavior according to the Fletcher criteria was determined in 25 of the 30 patients in our literature review: risk of pancreatic EGIST aggressive behavior was high in 17 cases. The remaining 8 cases were intermediate risk (n = 7; 28%) and low risk (n = 1; 4%).

The goal of surgical treatment, which is the most desirable treatment option for primary pancreatic EGISTs, is complete resection with microscopically clean (R0) margins[4,5,36]. Generally, primary surgery, surgical treatment following neoadjuvant chemotherapy, and debulking surgery for metastatic and/or advanced disease are considered in the surgical treatment of GISTs[2,5]. Surgical treatment selection depends on pancreatic EGIST localization. Standard or pylorus-preserving pancreaticoduodenectomy is the optimal treatment for pancreatic head tumors[4]. Duodenum-preserving pancreatic head resection may be performed for small tumors, low-grade tumors, or patients who cannot tolerate the Whipple procedure[4,36]. Conversely, radical surgical treatment may be the best option for preventing locoregional and/or distant metastases[13,15]. Regional lymph node metastases are rare in pancreatic EGIST cases, and routine systematic regional lymph node dissection is not indicated[4,13,16,18]. In our patient, EGIST was diagnosed after lymph node biopsy. Therefore, we suggest lymphadenectomy for cases of pathological lymphadenopathy observed during surgical exploration and for lymph node metastasis-positive cases based on intraoperative frozen section analysis. Depending on intraoperative findings and the surgeon's experience, pancreaticoduodenectomy, distal pancreatectomy with splenectomy, or partial pancreatic resection may be used for treating tumors in the pancreatic tail and corpus[13]. Nine and seven of the 30 patients underwent distal pancreatectomy with splenectomy, and the Whipple procedure, respectively.

The responses of GISTs to conventional chemotherapy and radiotherapy were very limited, being 10% and 5%, respectively[9,21]. These response rates changed when imatinib mesylate, an agent used for treating chronic myelogenous leukemia, was administered to a GIST case in the early 2000 s. Philadelphia chromosome-positive leukemia patients carry a mutation in the *BCR-ABL* gene, which is a KIT receptor family member. Additionally, the mutated *c-KIT* and *PDGFRA* genes seen in GISTs are members of the same family. Consequently, tyrosine kinase transmembrane receptors have been targeted in GIST treatment using two agents: imatinib mesylate and sunitinib malate. Imatinib was the first c-KIT tyrosine kinase inhibitor used for treating GISTs, specifically metastatic and unresectable GISTs, and was approved by the US Food and Drug Administration. Sunitinib was subsequently introduced for patients who could not tolerate imatinib or who were imatinib-resistant[2,23]. Recently, new tyrosine kinase inhibitors, such as nilotinib, sorafenib, dovitinib, and dasatinib, were introduced[5]. Despite the controversial approach of "which tyrosine kinase inhibitor, which patient and when", there is consensus for

initiating imatinib treatment in patients with high mitotic activity, gross dimensions, necrosis, and locoregional and/or distant metastasis[2,15]. Imatinib may be used as a neoadjuvant agent to downstage gross tumor volume for R0 resection and contributes to good prognosis[4]. Imatinib may be used as adjuvant treatment in cases with R1 (positive microscopic margin) or R2 (residual gross visible tumor) resection, risk of aggressive behavior, or poor prognostic features[4,5]. Similarly, imatinib treatment may be used as a primary modality in metastatic or unresectable cases to reduce tumor size, resulting in better prognosis[4]. Metastatic pancreatic EGIST cases benefit from debulking surgery, which increases the efficacy of imatinib[2]. The positive response to imatinib in patients with GISTs is 60%-70%, which can extend overall survival up to 5 years[4].

In conclusion, the term EGIST was introduced into the literature in the last decade. Debates on the similarities and differences between EGISTs and GISTs are ongoing. Despite their behavioral similarities, the initial asymptomatic period accounts for the gross tumor size of EGISTs. The lack of comprehensive case reports on EGISTs, including pancreatic EGISTs, limited our evidence-based review. Long-term follow-up studies of EGISTs are currently unavailable, limiting the amount of available information on tumor behavior. We are limited to the case reports that have been published to date and further immunohistochemical and genetic studies regarding EGIST behavior and response to treatment are needed.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract. The disease originates from neoplastic transformation of interstitial cells of Cajal or their precursors in the GI tract. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces. The morphological, histopathological, immunohistochemical and molecular profiles of EGISTs are similar to those of GISTs.

Research frontiers

The primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. To this end, the authors searched for studies on pancreatic GIST using different keyword combinations in the PubMed, MEDLINE, Google Scholar, and Google databases.

Terminology

GISTs are the most common mesenchymal tumors of the GI tract. EGISTs are defined as tumors originating from outside the GI tract. Imatinib mesylate was the first c-KIT tyrosine kinase inhibitor used to treat GISTs. The Fletcher criteria are used to estimate the risk of GIST aggressive behavior and metastasis using tumor size and mitotic counts.

Peer review

This paper comprises a case history, and a comprehensive review of the literature on pancreas GIST. The strength of the paper is that the authors have tried to collect available literature of the limited articles published on this topic.

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CASE REPORT

Gastric necrosis: A late complication of nissen fundoplication

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Abstract

Gastric necrosis is a rare condition because of the rich blood supply and the extensive submucosal vascular network of the stomach. "Gas-bloat" syndrome is a well known Nissen fundoplication postoperative complication. It may cause severe gastric dilatation, but very rarely an ischemic compromise of the organ. Other factors, such as gastric outlet obstruction, may concur to cause an intraluminal pressure enough to blockade venous return and ultimately arterial blood supply and oxygen deliver, leading to ischaemia. We report a case of a 63-year-old women, who presented a total gastric necrosis following laparoscopic Nissen fundoplication and a pyloric phytobezoar which was the trigger event. No preexisting gastric motility disorders were present by the time of surgery, as demonstrated in the preoperative barium swallow, thus a poor mastication (patient needed no dentures) of a high fiber meal (cabbage) may have been predisposing factors for the development of a bezoar in an otherwise healthy women at the onset of old age. A total gastrectomy with esophagojejunostomy was performed and patient was discharged home after a 7-d hospital stay with no immediate complications. We also discuss some technical aspects of the procedure that might be important to reduce the incidence of this complication.

Key words: Gastric dilatation; Gastric outlet obstruction; Necrosis; Fundoplication; Nissen operation

Core tip: Gastric necrosis is a rare condition because of the rich blood supply and the extensive submucosal vascular network of the stomach. "Gas-bloat" syndrome is a Nissen fundoplication postoperative complication that causes gastric dilatation, but very rarely an ischemic compromise of the organ. We report a case of a 63-year-old women, who presented a total gastric necrosis following laparoscopic Nissen fundoplication and we discuss technical aspects of the procedure that are important to prevent this complication.

Salinas J, Georgiev T, González-Sánchez JA, López-Ruiz E, Rodríguez-Montes JA. Gastric necrosis: A late complication of nissen fundoplication. *World J Gastrointest Surg* 2014; 6(9): 183-186 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i9/183.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i9.183

INTRODUCTION

The rich blood supply of the stomach preserves this viscera from ischemic events, even after the ligation of all the major vessels[1] (a. gastrica dextra, a. gastrica sinistra, a. gastro-omentalis dextra, a. gastro-omentalis sinistra and aa. gastricae breves). Notwithstanding this fact, acute gastric dilatation accompanied with or without gastric outlet obstruction[2-7], eating disorders[8-10] or gas-bloat syndrome are recognized causes of ischemic gastric necrosis.

The gas-bloat syndrome is defined as a variable group

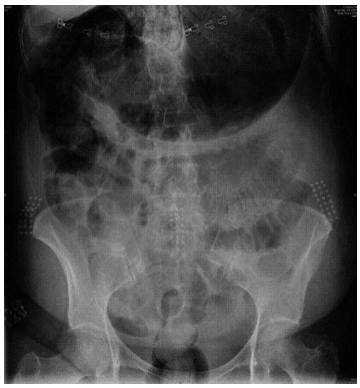

Figure 1 Plain abdominal radiography.

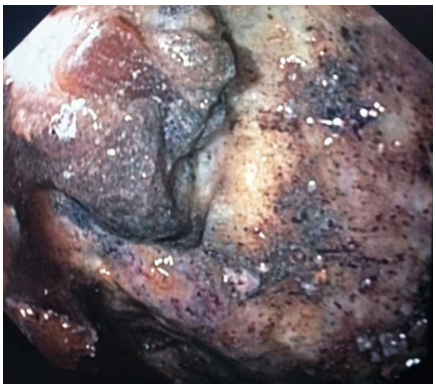

Figure 2 Gastric mucosal necrosis, endoscopic view.

of symptoms resulting from the inability to relieve gas from the stomach after fundoplication. It's incidence may vary from 1% to 85%[11]. Gastrointestinal gas may proceed either from an excessive production (carbohydrate or fat rich food, small intestinal bacterial overgrowth) or from an excess of swallowed air (disphagia secondary to orophagryngeal or esophageal motility disorders or anxiety disorders with inefficient chewing, gastroesophageal reflux disease, *etc.*). The predominant complaint is bloating, but other symptoms include abdominal distention, early satiety, nausea, upper abdominal pain, flatulence, inability to belch, and inability to vomit[11]. Antireflux surgery may contribute to the obstruction of gas blow into the esophagus by means of different mechanisms[12] (surgically altered physiology of the gastroesophageal junction, surgical injury to the vagus nerve, mechanic compression of the wrap), specially when associated to previous gastroesophageal motility disorders, such as delayed gastric emptying.

Delayed gastric emptying is a preexisting condition in many of the patients undergoing antireflux surgery. It is associated with gastroesophageal reflux disease (GERD) in up to 40% of patients, but Nissen fundoplication is known to accelerate gastric emptying and has a high rate of success controlling GERD-related symptoms[13], thus delayed gastric emptying is not a contraindication for antireflux surgery[14]. Nevertheless, a thoughtful preoperative assessment of esophagogastric motility with barium swallow is mandatory and may identify a subset of patients that will still have symptoms related to motility disorders postoperative.

Very few cases of near-total or total gastric necrosis following Nissen fundoplication have been reported. We present a case of gastric necrosis following laparoscopic Nissen fundoplication and pyloric obstruction by a phytobezoar.

CASE REPORT

A 63-year-old women was admitted to our Emergency Room with a history of sudden abdominal pain, without nausea or vomiting. No other symptoms were reported. Past medical history revealed acetylsalicylic acid intolerance, osteoporosis, supraspinatus rupture and gastroesophageal reflux disease secondary to a type I hiatal hernia, with a normal barium swallow esophagogastric motility pattern, a DeMeester of 33.1 and pathologic acid-clearance in pH-metry and a mild hypotonic lower esophageal sphincter in manometry, for which she underwent laparoscopic Nissen fundoplication 7 mo ago, with no postoperative complications and a 3-d hospital stay. The surgical record described a Rossetti-Nissen fundoplication without diversion of short gastric vessels (SGV), with a short wrap (3 cm) and suturing of the valve to the right crura. Treatment history revealed no medication that could interfere with upper digestive tract motility.

On physical examination, she was conscious, alert and oriented. Blood pressure was 123/75 mmHg with a pulse rate of 76/min. The abdomen was distended, painful to palpation with generalized peritonism and involuntary guarding in the epigastrium. Bowel sounds were diminished. Laboratory findings revealed: hemoglobin, 14.6 g/dL; hematocrit, 44.7%; white blood cell count, 18900/μL (with 15500 neutrophils); platelet count, 372000/μL; lactic dehydrogenase and amylase were elevated to 251 U/L (normal, 87-246 U/L) and 564 U/L (normal, 25-115 U/L), respectively. Arterial blood gases showed a metabolic acidosis with a blood pH of 7.23.

The patient was taken to the radiology department and plain abdominal films were performed (Figure 1). A gastroscopy was performed after X-rays, since a nasogastric tube couldn't be placed, and a wide area of mucosal necrosis was found in the posterior wall of the lesser curvature (Figure 2). In the operating room an extreme gastric dilatation was found with ischemic changes. The lesser sac was opened and dissection of the posterior gastric surface confirmed endoscopic findings. An anterior longitudinal gastrotomy was performed and trapped air was released. Suction of the gastric chamber through the gastrotomy revealed a phytobezoar in the pyloric channel. Total gastrectomy (Figure 3) with esophagojejunostomy and Roux-en-Y reconstruction was performed. The pathology (Figure 4) revealed a transmural submassive ischemic necrosis with intravascular thrombi. After a postoperative period without complications, the patient was successfully discharged home.

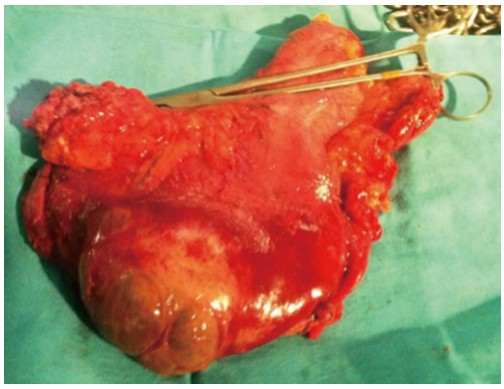

Figure 3 Transmural gastric necrosis, total gastrectomy surgical specimen.

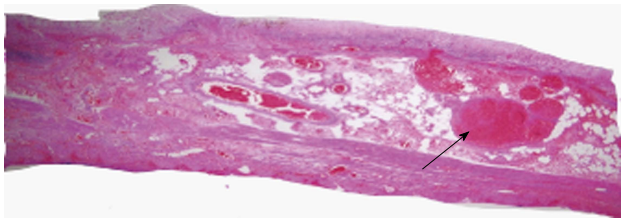

Figure 4 Submassive transmural gastric necrosis with intravascular thrombi (arrow); Hematoxilin-Eosin stain.

DISCUSSION

Gastric dilatation is a minor postoperative complication that can eventually occur after major surgery. This condition usually resolves spontaneously or with the insertion of a nasogastric tube for gastric decompression. On the contrary, ischemic necrosis following extreme gastric dilatation is a very rare phenomenon and requires urgent diagnosis and surgical treatment.

Clinical manifestations of the "gas-bloat" syndrome (abdominal pain, distension, tympanic percussion, *etc.*) are common to many other abdominal pathologies, that without a full comprehension of the surgical history, may delay the diagnosis with the increased morbidity and mortality that this entails. Early surgical consult for the evaluation of patients with abdominal pain and surgical history is vital in the emergency room context and decisive for patient outcome.

In the Nissen antireflux procedure, compression of the distal oesophagus by the gastric wrap is required to ensure the one-way valve effect that prevents gastric reflux. Expelling trapped air and belching is therefore sometimes hindered, resulting in a progressive gastric dilatation. Thanks to the anterograde propulsion, which works as an exhaust valve, this condition is intermittent. When anterograde propulsion is totally or partially blocked, gastric distension progressively tightens the periesophageal wrap, thus increasing the intragastric pressure and compromising blood flow. Some studies have shown that an intragastric pressure greater than 20-30 cm H_2O is necessary to cause the occlusion of the gastric luminal blood circulation[15]. Cases of gastric necrosis following acute small bowel obstruction based on adhesions and gastric outlet obstruction based on antral gastric cancer and trichophytobezoar after an antireflux technique[3-5] have been reported. In infants, this rare post Nissen complication has also been described[16]. In the case we present, the trigger event was a phytobezoar causing pyloric obstruction.

Since 1955, when Rudolph Nissen performed his first fundoplication, many other procedures that try to reduce the incidence of postoperative complications, including the "gas-bloat" syndrome, have been developed, without a loss of effectiveness in preventing gastroesophageal reflux disease, as demonstrated in several randomized controlled trials and long case series[17-20].

Nevertheless, due to the lack of long-term effectiveness data, it is hard to recommend one type of fundoplication over an other, and Rossetti-Nissen laparoscopic fundoplication still a valid and widespread procedure with a low rate of postoperative complications[17], when performed by trained surgeons. Some technical aspects during a Nissen fundoplication are important, specially for the novice surgeon, and should be considered to avoid surgery-related complications, including the "gas-bloat" syndrome. This may include a short wrap (typically no more than 2 cm), instead of a long one, or the systematic division of the SGV to facilitate a tension-free wrapping[21,22]. The latter is controversial and some prospective randomized trials have proven the contrary: a higher incidence of gas-bloat syndrome when the SGV are divided[23]. In the case presented, no division of the gastric short vessels was performed, but a floppy fundoplication was achieved, and the patient referred no complaints in follow-ups. So the authors do not consider that the preservation of the gastric short vessels was a contributing factor in this particular case.

An important issue to be also remarked is the importance of identifying patients with anxiety and comfort or binge eating conducts, which could have been disregarded in the preoperative consult, and that could potentially have higher risk of complications in the long term. Antidepressant medication and early psychiatric consult might be necessary.

COMMENTS

Case characteristics

The only symptom referred by the patient was sudden and intense pain in epigastrium.

Clinical diagnosis

Main clinical findings were upper abdominal distension, tympanic percussion and peritoneal irritation.

Differential diagnosis

Differential diagnosis was mainly based on past surgical history: acute gastric dilatation *vs* small bowell obstruction.

Laboratory diagnosis

Laboratory findings were congruent with an acute inflammatory process with poor splacnic perfusion: high leukocyte count and high lactic dehydrogenase and amylase.

Imaging diagnosis

Plain abdominal X-ray is more than adequate to diagnose gastric distension, but a computed tomography-scan may be also helpful to note ischemic changes

and involvement.

Pathological diagnosis

Routine Hematoxylin-Eosin stain was performed to find out ischemic tissue injuries.

Treatment

Surgery was mandatory in this case based on clinical and analytical findings, and a total gastrectomy was performed.

Experiences and lessons

Antireflux surgery, although it might not be of extreme complexity, it is not free of severe complications and common pitfalls such as long or tightened wraps should be avoided. Also, patients with antireflux surgery and anxiety symptoms or eating disorders should be recognized and properly treated with psychiatric consult if necessary.

Peer review

The case report is useful as it serves to highlight that fundoplication can have serious complications.

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CASE REPORT

Retroanastomotic hernia after Moynihan's gastroenterostomy

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Abstract

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to delayed identification which precludes immediate surgical reduction. In this report, we present a 77-year-old man with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

Key words: Retroanastomotic hernia; Moynihan's gastroenterostomy; Intestinal obstruction

Core tip: Retroanastomotic hernia is a rare but fatal condition. Preoperative diagnosis by ultrasound and/or computerized tomography is difficult and sometimes confusing. Early surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

Karaman K, Yalkin O, Ercan M, Demir H, Altintoprak F, Zengin I. Retroanastomotic hernia after Moynihan's gastroenterostomy. *World J Gastrointest Surg* 2014; 6(9): 187-189 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i9/187.htm
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INTRODUCTION

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to a delay in identification which precludes immediate surgical reduction[1]. Since Petersen[2] provided the first detailed description of a retroanastomotic hernia known as Petersen's hernia in 1900, there have been few case reports or case series in the literature referring to this entity. In this report, we present a 77-year-old man with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

CASE REPORT

A 77-year-old man presented with a sudden onset of acute abdominal pain accompanied by nausea and vomiting. The physical examination revealed rebound tenderness with abdominal distention. Abdominal computed tomography showed edematous bowel wall thickening in proximal small bowel segments and dense fluid collection in the right upper quadrant which was considered an indication of visceral organ perforation (Figure 1A). The patient underwent a subtotal gastrectomy for duodenal ulcer 14 years ago. During explorative laparotomy, a retroanastomotic hernia of the efferent loop segments, passing from right to left through the orifice between the transverse colon and the antecolic, antiperistaltic gastrojejunostomy anastomosis (Moynihan type), was found (Figure 1B-D). The herniated bowel segments were reduced and the defect was closed with running sutures. Viability of the ischemic bowel segments improved after application of warm pads and the abdomen was closed without further intervention. The postoperative course was un-

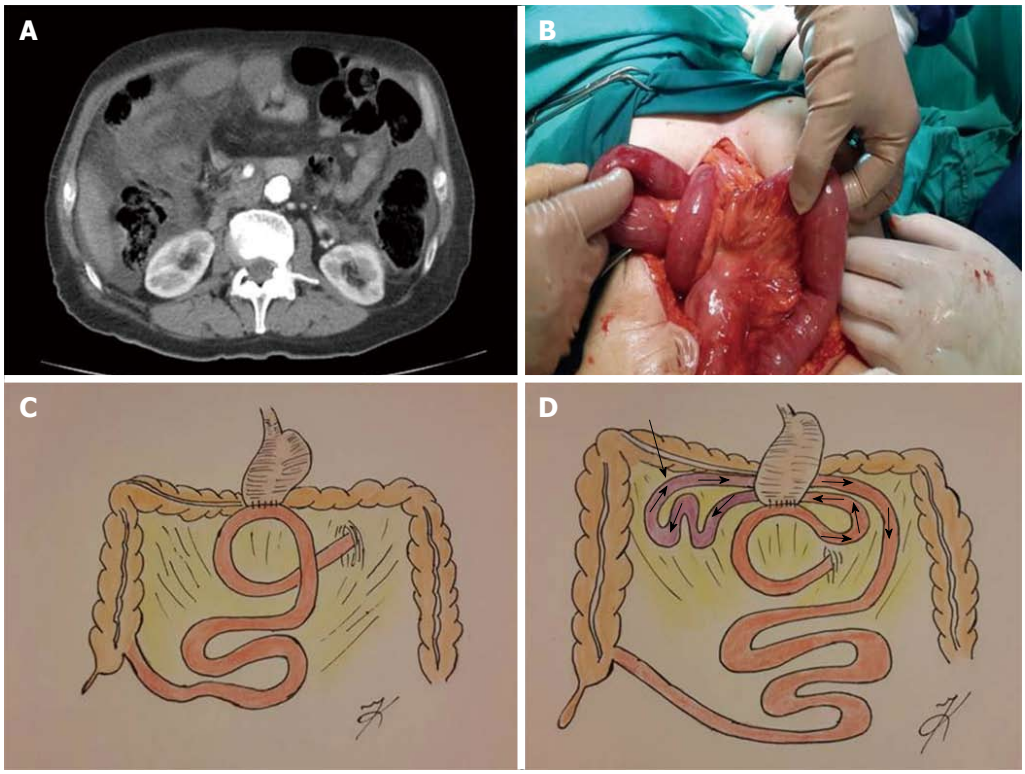

Figure 1 Illustration of diagnosis and treatment of the present case. A: Abdominal computed tomography image of the retroanastomotic hernia; B: Intraoperative image of the retroanastomotic herniation; C: Illustration of the original operation (Moynihan's gastroenterostomy); D: Illustration of the retroanastomotic herniation of the present case with a black arrow showing the incarcerated bowel segments of the efferent loop.

eventful and the patient was discharged on the fifth postoperative day.

DISCUSSION

Herniation of intestinal loops through the defect between the small bowel limbs can occur after any type of gastrojejunostomy[3,4]. Half of all retroanastomotic hernias occur within the first postoperative month; more than half of the remaining during the first year, and a small percentage even later[5]. Efferent loop hernias occur three times more than those involving the afferent loop. For afferent loop hernias, pain is localized to the epigastric region and is constantly sudden in onset. Vomiting is infrequent and bile is almost absent, if not at all. On the other hand, in efferent loop hernias, abdominal pain is more generalized and colicky, and vomiting with bile stained material is common[1]. Preoperative diagnosis by ultrasound and/or computed tomography is difficult and sometimes confusing: the most frequently detected signs are mural thickening and dilatation of the herniated bowel loops[6].

Efferent loop hernias usually occur from right to left. In the present case, however, the direction of the herniation was from left to right, which may be related to the type of gastroenterostomy (Moynihan type). Another important characteristic of the present case was the long duration of the disease without any signs.

In conclusion, retroanastomotic hernias, though rare, are a potentially fatal condition. Early surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

COMMENTS

Case characteristics

A 77-year-old man presented with retroanastomotic herniation of the efferent loop segments that occurred 14 years after a Moynihan's gastroenterostomy.

Clinical diagnosis

Retroanastomotic herniation of efferent loop segments after the antecolic gastrojejunostomy anastomosis.

Differential diagnosis

Acute abdomen due to visceral organ perforation.

Laboratory diagnosis

White blood cells: 16.400/mm^3; hemoglobin: 121.0 g/L. Metabolic panel and liver function test were within normal limits.

Imaging diagnosis

Computed tomography showed edematous bowel wall thickening in proximal small bowel segments and dense fluid collection in the right upper quadrant which was considered an indication of visceral organ perforation.

Treatment

Reduction of the herniated efferent loop segments and primary closure of the hernia defect.

Related reports

There have been few case reports or case series in the literature referring to this entity.

Term explanation

Retroanastomotic hernias after gastroenterostomies-either antecolic or retrocolic-are extremely rare but are associated with high mortality rates due to a delay in identification which precludes immediate surgical reduction.

Experiences and lessons

Retroanastomotic hernias, though rare, are a potentially fatal condition. Early

surgery is the key to decreasing mortality. The use of a short afferent loop and closure of the retroanastomotic space would decrease the incidence of these hernias.

Peer review

This article is referring a rare complication of gastroenterostomy anastomosis and discusses the possible causes and preventive approaches.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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