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FIELD OF VISION

Is there a role for arterial reconstruction in surgery for pancreatic cancer?

Reena Ravikumar, David Holroyd, Giuseppe Fusai

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Abstract

Surgery remains the only potentially curative treatment for patients with pancreatic cancer. Locally advanced pancreatic cancer with vascular involvement remains a surgical challenge because high perioperative risk and the uncertainty of a survival benefit. Whilst portal vein resection has started to gather momentum because the perioperative morbidity and long term survival is comparable to standard pancreatectomy, there isn't yet a consensus on arterial resections. There have been various reports and case series of arterial resections in pancreatic cancer, with mixed survival results. Mollberg *et al* have appraised the heterogeneous published literature available on arterial resection in pancreatic cancer in an attempt to compare this to standard pancreatectomy. In this article, we discuss the results of this systematic review and meta-analysis, and the limitations associated with analysing results from heterogenous data. We have outlined the important features in surgery for pancreatic cancer and specifically to arterial resections, and compared arterial resections to the published literature on venous resections.

Key words: Arterial resection; Pancreatic cancer; Vascular resection; Hepatic artery; Coeliac axis; Pancreatectomy

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COMMENTARY ON HOT TOPICS

The systematic review and meta-analysis on arterial resection during pancreatectomy by Mollberg *et al*[1] is a very timely and current paper. They report perioperative and survival outcomes associated with arterial resection during pancreatectomy for pancreatic cancer, compared to pancreatectomy alone.

Worldwide, pancreatic cancer is the 13th most common cancer, but the eight most common cause of cancer death with little improvement in survival over the last few decades[2]. Surgical resection remains the only hope for cure in these patients. However, many of these patients are diagnosed at a late stage because of the nature of the disease and surgical resection with a curative intent is rarely possible. Fortner[3], first described a "regional pancreatectomy" involving total pancreatectomy, radical lymph node clearance, combined portal vein resection (Type 1) and/or combined arterial resection and reconstruction (Type 2). This was found to be associated with unacceptably high morbidity and mortality rates, and was abandoned. More lately, pancreatectomy with portal vein resection and reconstruction has began to gather momentum as studies demonstrated acceptable morbidity and long term survival rates comparable to standard pancreaticoduodenectomy (PD)[4-6]. In recent years, the morbidity and mortality rates between standard PD and pancreatico-duedenectomy with vascular resection have been similar[4,5,7,8]. Isolated venous involvement

is no longer a contraindication to PD when performed by experienced surgeons at high volume centers as part of a multidisciplinary approach to localized pancreatic cancer[9] arterial resection, however, has remained highly controversial. Current oncological guidelines suggest that pancreatic tumours invading arterial structures render these cancers inoperable[10]. Nevertheless, attempts at resection involving reconstruction of the main arteries such as the coeliac axis, hepatic artery and superior mesenteric artery (SMA) have been reported, albeit in small case series[8,11-16].

The study population for the meta-analysis is the largest in the published literature despite the unsurprising heterogeneity of the 26 studies that met inclusion criteria; a limitation acknowledged by the authors. In total, 366 patients underwent pancreatectomy with concomitant aprtic regurgitation (AR) out of a total of 2609 patients that were included in the study. All data were non-controlled, collected retrospectively, over a prolonged study period (1973-2010), with a high proportion of procedures performed pre-2000, and with a high risk of bias in 22/26 studies. In addition, as the authors point out, the median number of patients per study is 12.5, suggesting a pooled analysis may be a more suitable method of data evaluation[1].

There was considerable heterogeneity in the types of surgical procedures performed across the studies included in Mollberg's systematic review, including cases where arterial resection was performed in combination with venous resection and/or extended lymphadenectomy. Mollberg *et al*[1] found that perioperative morbidity was significantly increased in patients undergoing concomitant AR compared to those undergoing pancreatectomy alone (OR = 2.17, 95%CI: 1.26-3.75, $P = 0.006$; $I^2 = 35\%$), with a significantly higher re-operation rate (OR = 3.28, 95%CI: 1.68-6.41, $P < 0.001$; $I^2 = 33\%$) and with a 5 times greater perioperative mortality risk in the AR group (OR = 5.04, 95%CI: 2.69-9.4, $P < 0.0001$; $I^2 = 24\%$). This can be explained by the complexity and technical challenge associated with an arterial resection including the risk of bowel ischaemia. They also found a greater perioperative mortality rate amongst patients undergoing arterial resection in comparison to venous resection in their subgroup analyses (OR = 8.87, 95%CI: 3.4-23.13, $P < 0.0001$; $I^2 = 5\%$).

There was no significant difference in the incidence of lymph node metastases between patients undergoing pancreatectomy with and without AR (OR = 1.39, 95%CI: 0.85-2.27, $P = 0.19$; $I^2 = 0\%$). There was also no difference found in R0 resection rates between the 2 groups when analysing 209 patients in 15 studies who provided this data. However, the exclusion of a study by Boggi *et al*[14] by sensitivity analysis indicated a lower R0 resection rate in the AR group with low heterogeneity. However, the role of resection margin status as a prognostic indicator remains controversial due to the lack of uniformity of pathology reporting for pancreatic cancer[17,18].

Median survival at 1, 3 and 5 years for patients undergoing AR during pancreatectomy was 49.1%, 8.3% and 0%, respectively. Meta-analysis of survival data demonstrated that there was a significantly lower chance of long term survival for patients undergoing pancreatectomy with concomitant AR compared to pancreatectomy. This is in contrast to survival outcomes for patients with pancreatic cancer involving the portal vein where the overall survival is similar in the resection groups (with and without vein resection) and significantly greater than patients having a palliative bypass[4,5,19,20]. The median 1-, 3- and 5-year survival rates for patients with AR were significantly reduced. This persisted even after excluding the study by Boggi *et al*[14] for heterogeneity following a sensitivity analysis. The authors therefore compared AR to palliative non-surgical therapy, which was reported in 6 studies. This showed a significantly higher 1- and 2-year survival for patients undergoing AR after excluding a study by Wang for heterogeneity. However, as explained by the authors, the non-controlled nature of these studies could have meant that the patients who did not undergo resection could have had an inherently worse prognosis, with more advanced tumours, compared to those undergoing AR.

This study is a very comprehensive analysis of the data that are currently available concerning arterial resection during pancreatectomy. It demonstrates significantly increased peri-operative morbidity and mortality, combined with significantly poorer survival outcomes at 1, 3 and 5 years. The authors conclude that the need for arterial resection in itself is the actual risk factor for increased perioperative death. However, they also suggest that in the absence of other treatment for tumours involving the SMA, with careful patient selection, arterial resection may be justified in a small cohort of patients. In addition, the authors also suggest a prospective registry to allow accurate analysis of outcome data for patients undergoing an arterial resection. We would augment this idea by suggesting a protocol detailing patient eligibility for arterial resection as a first step towards determining the suitability of this highly complex procedure, which may only be relevant to a specific subset of patients.

REFERENCES

1 **Mollberg N**, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011; **254**: 882-893 [PMID: 22064622 DOI: 10.1097/SLA.0b013e31823ac299]

2 Cancer worldwide -the glocal picture. Cancerstats. Available from: URL: http: //www.cancerresearchuk.org/cancer-info/cancerstats/world/the-global-picture/cancer-overall-world

3 **Fortner JG**. Regional resection of cancer of the pancreas: a new surgical approach. *Surgery* 1973; **73**: 307-320 [PMID: 4265314]

4 **Tseng JF**, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Gomez HF, Sun CC, Crane CH, Wolff RA, Evans DB. Pancreaticoduodenectomy with vascular resection: margin

status and survival duration. *J Gastrointest Surg* 2004; **8**: 935-949; discussion 949-950 [PMID: 15585381 DOI: 10.1016/j.gassur.2004.09.046]

5 **Yekebas EF**, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008; **247**: 300-309 [PMID: 18216537 DOI: 10.1097/SLA.0b013e31815aab22]

6 **Chua TC**, Saxena A. Extended pancreaticoduodenectomy with vascular resection for pancreatic cancer: a systematic review. *J Gastrointest Surg* 2010; **14**: 1442-1452 [PMID: 20379794 DOI: 10.1007/s11605-009-1129-7]

7 **Banz VM**, Croagh D, Coldham C, Tanière P, Buckels J, Isaac J, Mayer D, Muiesan P, Bramhall S, Mirza DF. Factors influencing outcome in patients undergoing portal vein resection for adenocarcinoma of the pancreas. *Eur J Surg Oncol* 2012; **38**: 72-79 [PMID: 22054617 DOI: 10.1016/j.ejso.2011.08.134]

8 **Martin RC**, Scoggins CR, Egnatashvili V, Staley CA, McMasters KM, Kooby DA. Arterial and venous resection for pancreatic adenocarcinoma: operative and long-term outcomes. *Arch Surg* 2009; **144**: 154-159 [PMID: 19221327 DOI: 10.1001/archsurg.2008.547]

9 **Christians KK**, Lal A, Pappas S, Quebbeman E, Evans DB. Portal vein resection. *Surg Clin North Am* 2010; **90**: 309-322 [PMID: 20362788 DOI: 10.1016/j.suc.2009.12.001]

10 Available from: URL: http: //www.nccn.org/professionals/physician_gls/f_guidelines.asp

11 **Katz MH**, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008; **206**: 833-846; discussion 846-848 [PMID: 18471707 DOI: 10.1016/j.jamcollsurg.2007.12.020]

12 **Stitzenberg KB**, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, Hoffman JP. Survival after pancreatectomy with major arterial resection and reconstruction. *Ann Surg Oncol* 2008; **15**: 1399-1406 [PMID: 18320285 DOI: 10.1245/s10434-008-9844-y]

13 **Amano H**, Miura F, Toyota N, Wada K, Katoh K, Hayano K, Kadowaki S, Shibuya M, Maeno S, Eguchi T, Takada T, Asano T. Is pancreatectomy with arterial reconstruction a safe and useful procedure for locally advanced pancreatic cancer? *J Hepatobiliary Pancreat Surg* 2009; **16**: 850-857 [PMID: 19844653 DOI: 10.1007/s00534-009-0190-7]

14 **Boggi U**, Del Chiaro M, Croce C, Vistoli F, Signori S, Moretto C, Amorese G, Mazzeo S, Cappelli C, Campani D, Mosca F. Prognostic implications of tumor invasion or adhesion to peripancreatic vessels in resected pancreatic cancer. *Surgery* 2009; **146**: 869-881 [PMID: 19744432 DOI: 10.1016/j.surg.2009.04.029]

15 **Bachellier P**, Rosso E, Lucescu I, Oussoultzoglou E, Tracey J, Pessaux P, Ferreira N, Jaeck D. Is the need for an arterial resection a contraindication to pancreatic resection for locally advanced pancreatic adenocarcinoma? A case-matched controlled study. *J Surg Oncol* 2011; **103**: 75-84 [PMID: 21105000 DOI: 10.1002/jso.21769]

16 **Yamamoto Y**, Sakamoto Y, Ban D, Shimada K, Esaki M, Nara S, Kosuge T. Is celiac axis resection justified for T4 pancreatic body cancer? *Surgery* 2012; **151**: 61-69 [PMID: 22088810 DOI: 10.1016/j.surg.2011.06.030]

17 **Verbeke CS**, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. *Br J Surg* 2006; **93**: 1232-1237 [PMID: 16804874 DOI: 10.1002/bjs.5397]

18 **Fusai G**, Warnaar N, Sabin CA, Archibong S, Davidson BR. Outcome of R1 resection in patients undergoing pancreatico-duodenectomy for pancreatic cancer. *Eur J Surg Oncol* 2008; **34**: 1309-1315 [PMID: 18325723 DOI: 10.1016/j.ejso.2008.01.017]

19 **Tseng JF**, Tamm EP, Lee JE, Pisters PW, Evans DB. Venous resection in pancreatic cancer surgery. *Best Pract Res Clin Gastroenterol* 2006; **20**: 349-364 [PMID: 16549332 DOI: 10.1016/j.bpg.2005.11.003]

20 **Abramson MA**, Swanson EW, Whang EE. Surgical resection versus palliative chemoradiotherapy for the management of pancreatic cancer with local venous invasion: a decision analysis. *J Gastrointest Surg* 2009; **13**: 26-34 [PMID: 18946644 DOI: 10.1007/s11605-008-0648-y]

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BRIEF ARTICLE

Hepatic histopathology and postoperative outcome after preoperative chemotherapy for Chinese patients with colorectal liver metastases

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Abstract

AIM: To assess the effects of preoperative treatment on the hepatic histology of non-tumoral liver and the postoperative outcome.

METHODS: One hundred and six patients underwent hepatic resection for colorectal metastases between 1999 and 2009. The surgical specimens were reviewed with established criteria for diagnosis and grading of pathological hepatic injury. The impact of preoperative therapy on liver injury and postoperative outcome was analyzed.

RESULTS: Fifty-three patients (50%) received surgery alone, whereas 42 patients (39.6%) received neoadjuvant chemotherapy and 11 (10.4%) patients received preoperative hepatic artery infusion (HAI). Chemotherapy included oxaliplatin-based regimens (31.1%) and irinotecan-based regimens (8.5%). On histopathological analysis, 16 patients (15.1%) had steatosis, 31 (29.2%) had sinusoidal dilation and 20 patients (18.9%) had steatohepatitis. Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone (42.4% *vs* 20.8%, $P = 0.03$); however, the perioperative complication rate was not significantly different between the oxaliplatin group and surgery group (27.3% *vs* 13.2%, $P = 0.1$). HAI was associated with more steatosis, sinusoidal dilation and steatohepatitis than the surgery group, with higher perioperative morbidity (36.4% *vs* 13.2%, $P = 0.06$) and mortality (9.1% *vs* 0% $P = 0.02$).

CONCLUSION: Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, the preoperative oxaliplatin had no significant impact on perioperative outcomes. HAI can cause pathological changes and tends to increase perioperative morbidity and mortality.

Key words: Drug liver injury; Preoperative chemotherapy; Hepatic artery infusion; Sinusoidal dilation

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common

causes of cancer death in the Western world, ranking second in Europe and third in the United States[1]. The incidence of CRC in China is lower than that in the West, but has increased in recent years[2,3] and has become a substantial burden in China. Some studies have reported changes in the characteristics of colorectal cancers in China[4,5]. Approximately 50% of patients with colorectal cancer develop liver metastases at some point during the course of their disease[6,7]. Surgical resection remains the first choice of treatment, with a 25%-40% long-term survival rate[8,9]. However, only 15%-20% of patients with colorectal liver metastases are suitable for surgical resection[10]. Chemotherapy is the first choice of treatment for unresectable patients but it is very rare for patients treated with chemotherapy alone to survive longer than 5 years.

Neoadjuvant chemotherapy has been evaluated in patients with initially resectable liver metastases. The rationale for using preoperative chemotherapy in patients with initially resectable disease includes an opportunity to demonstrate regimen-specific efficacy, as well as allowing time to identify those patients who will progress and who therefore may not benefit from liver resection. In addition, preoperative chemotherapy may decrease the magnitude of resection needed[11].

Although the use of new chemotherapeutic agents has a number of theoretical benefits, concern about liver injury after surgery led investigators to examine the impact of chemotherapy[12-16]. In the current study, we analyze the histopathological changes associated with preoperative chemotherapy and report the postoperative outcome.

In addition, hepatic artery infusion (HAI) has been increasingly used in China as a palliative treatment of unresectable colorectal metastases (CRM) or the edge of the liver function in an effort to reduce lesion size and thus make surgery feasible when the remnant liver is insufficient in size, based on cross-sectional imaging volumetrics. Therefore, we also collected data to evaluate whether HAI before surgery can have an impact on hepatic histopathology.

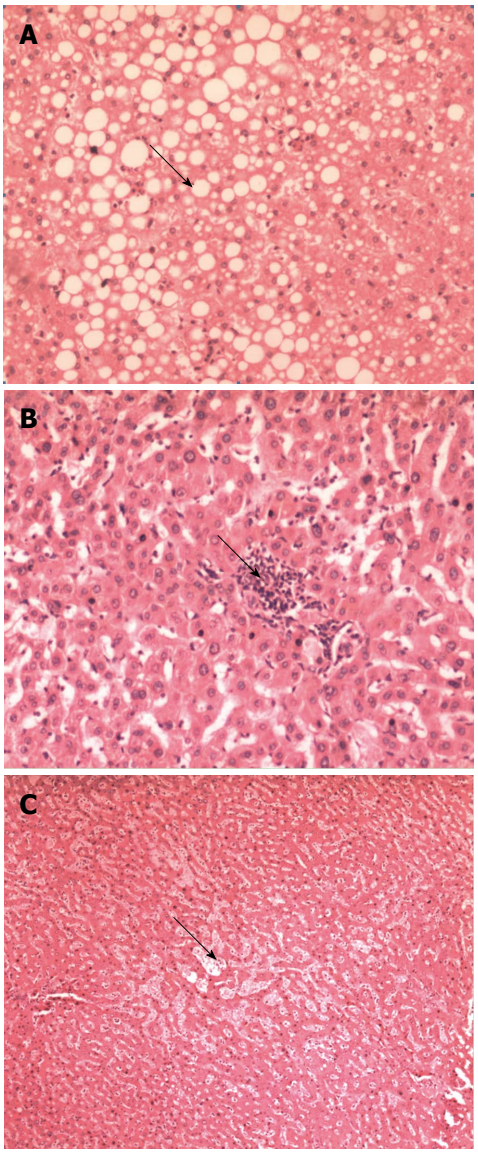

Figure 1 Histopathological findings. A: Severe steatosis. Large drop of fat (arrow) in the majority of hepatocytes, HE, 100 ×; B: Example of steatohepatitis showing the foci (arrow) of inflammation among the hepatocytes, HE, 100 ×; C: Grade 3 sinusoidal dilation involved the complete lobule, HE, 40 ×.

MATERIALS AND METHODS

A retrospective review was undertaken on patients who underwent hepatic surgery for CRM with a curative intent at Peking University Cancer Hospital between January 1999 and April 2009. Hepatic resections were defined according to the Brisbane terminology[17,18]. Patients were divided into the following four groups based on their preoperative therapy: (1) no preoperative therapy; (2) Oxaliplatin-based chemotherapy with fluorouracil (FU) or Xeloda; (3) Irinotecan-based chemotherapy plus FU; and (4) preoperative HAI. Only patients who received regional therapy with HAI were included in the HAI group.

Standard demographic data were collected on all patients, including type and duration of preoperative treatment, details of the resection, estimated blood loss (EBL), characteristics of the resected tumor, postoperative morbidity and 90 d mortality.

The archival slides (original formalin-fixed, paraffin-embedded and HE staining) from those resected hepatic specimens were blindly reviewed by a pathologist (Zhao AL). The histopathological findings in the non-tumoral liver tissue were evaluated semi-quantitatively as follows: (1) degree of steatosis was graded as none, mild (< 30%), moderate (≥ 30% to 50%) or severe (≥ 50%; Figure 1A); (2) steatohepatitis was graded as defined by Kleiner *et al*[19] based on steatosis (score 0: < 5%; 1: 5% to 33%; 2: > 33% to 66%; and 3: > 66%), lobular inflammation (score 0: no foci; 1: one foci; 2: two to four foci; and 3: > four foci per 200 × field) and ballooning (score 0: none; 1: few balloon cells; and 2: many cells/prominent ballooning, Figure 1B); and (3) sinusoidal injury was graded according to an established grading system of sinusoidal dilation (grade 0: absent; grade 1: centrilobular involve-

Table 1 Clinical and pathological features of patients (*n* = 106) *n* (%)

Variable	Patients
Sex	
Female	56 (52.8)
Male	50 (47.2)
Site of primary tumor	
Colon	55 (51.9)
Rectum	51 (48.1)
Hepatic metastases	
Median	3
Solitary	61 (57.5)
Multiple	45 (42.5)
Metastases type	
Synchronous	44 (41.5)
Metachronous	62 (58.5)
Extent of hepatic resection	
Minor (1-2 segment)	81 (76.4)
Major (≥ 3 segment or hemihepatectomy)	25 (23.6)

Median age of patients is 60 yr.

ment limited to one-third of the lobular surface; grade 2: centrilobular involvement extending in two-thirds of the lobular surface; grade 3: complete lobular involvement)[12] (Figure 1C). Hepatic injury was defined as steatosis more than 30%, steatohepatitis Kleiner score ≥ 4 and/or grade 2-3 sinusoidal dilation.

Statistical analysis

Summary statistics were performed using the χ^2 test and Fisher's exact test for comparing categorical variables; the Kruskal-Wallis test was used to compare continuous variables among the treatment groups. The odds ratios (OR) and the 95%CI were estimated and *P* value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS software, version 9.0.

RESULTS

Table 1 presents the clinicopathological features of the 106 patients in the study. A total of 106 patients were included in the analysis. There were 50 (47.2%) men and 56 (52.8%) women and the median patient age was 60 years (range 32-79 years). The presentation of hepatic metastases was metachronous in most patients (*n* = 62; 58.5%), while synchronous metastases accounted for 41.5%. The median number of hepatic metastases was 3 (range 1-5) and the median size of the largest lesion was 4 cm (range 0.7-22 cm).

At the time of the operation, the extent of hepatic resection was less than 3 segments or hemihepatectomy in 81 patients (76.4%) and a hemihepatectomy or more than 3 segments removal in 25 patients (23.6%). The median EBL was 200 mL (range 50-3000 mL). The median EBL in the preoperative chemotherapy arm was 575 mL, which was obviously higher than those without preoperative treatment (200 mL).

A total of 42 patients received neoadjuvant chemotherapy therapy, consisting of oxaliplatin plus FU regimen (33, 31.1%) and irinotecan plus FU regimen (9, 8.5%). While 11 (10.4%) patients received preoperative HAI before surgical treatment of the hepatic metastases, in which 8 patients received Cisplatin plus Epirubicin, three patients received oxaliplatin plus FU/CF. Of the 42 patients who received preoperative chemotherapy, the median duration was 5 cycles with 2-3 wk per cycle (range 2-10 cycles). The median duration of the HAI group was 3 cycles with 1 mo per cycle (range 1-3 mo). In general, the tumor characteristics and surgery details were similar among all preoperative treatment groups (Table 2). There was also no significant difference between groups with regard to age, gender, site of primary tumor, number of hepatic CRM, EBL or hepatic CRM tumor size (all $P > 0.05$). Patients who received HAI before surgery tended to have less EBL than other groups.

The overall perioperative complication rate was 18.9%. Thirteen patients (12.3%) suffered from hepatic complications, including liver failure (*n* = 3), hepatic insufficiency (*n* = 2), bile leaks (*n* = 9) and hepatic abscess (*n* = 1). Non-hepatic complications occurred in 11 patients (10.3%); there were 6 pulmonary complications (5.7%; pleural effusion, *n* = 6), 1 cardiovascular complications (0.94%; rapid atrial fibrillation, *n* = 1), 1 stress ulcer (0.94%) and 1 pancreatic fistula (0.94%), 2 peritoneal effusion (1.8%) and 1 with abdominal infectious complications (0.94%). Overall, the perioperative complication rate was similar between the no-chemotherapy group (13.2%) and the chemotherapy group (21.4%) ($P = 0.29$). In addition, patients who received HAI tended to have more postoperative morbidity (36.4% *vs* 13.2%, $P = 0.06$) and mortality (9.1% *vs* 0% $P = 0.02$) than those who received no preoperative chemotherapy. The complication rate did not differ with a different type of preoperative therapy (HAI 36.4%; irinotecan 0%; oxaliplatin 27.3%) ($P = 0.07$).

During the final pathological analysis of the resected specimen, hepatic injury was shown in 51 patients (48.1%). Steatosis more than 30% was identified in 16 patients (15.1%), grade 2 to 3 sinusoidal dilation in 31 patients (29.2%) and steatohepatitis Kleiner score ≥ 4 in 20 patients (18.9%). Preoperative chemotherapy is associated with pathological liver injury compared with non treatment before surgery (57.1% *vs* 35.8%, $P = 0.038$; OR: 2.39; 95%CI: 1.0-5.4). When patients were stratified according to the duration of chemotherapy (1 to 5, 6 to 10 cycles), the rate of hepatic injury increased over time in patients who received preoperative chemotherapy (76.2% *vs* 38.1%, $P = 0.01$). In Table 3, specifics on hepatic injury stratified by preoperative therapy are listed. Neither oxaliplatin nor irinotecan as neo-adjuvant chemotherapy before liver resection was associated with an increased rate of steatosis. The type of chemotherapy regimen used was associated with distinct patterns of liver injury: oxaliplatin was associated with grade 2 to 3 sinusoidal dilation compared with no chemotherapy (42.4% *vs* 20.8%, respectively, $P = 0.03$; OR = 2.8; 95%CI: 0.97-8.2). Patients receiving irinotecan also tended to have a higher likelihood of steatohepatitis compared with non treatment before surgery (33.3% *vs* 11.3%, $P = 0.08$), although the *P*

Table 2 Patient clinicopathological characteristics stratified by whether they received chemotherapy *n* (%)

Variable	Patients (*n* = 106)	Chemotherapy (*n* = 53)	Oxaliplatin (*n* = 33)	Irinotecan (*n* = 9)	HAI (*n* = 11)	*P* value
Mean age, yr	60	59.8	56.9	56.9	54.2	0.26
Gender						
Female	56 (52.8)	29 (54.7)	16 (48.5)	5 (55.6)	6 (54.5)	0.95
Male	50 (47.2)	24 (45.3)	17 (51.5)	4 (44.4)	5 (45.5)	
Site of primary tumor						
Colon	55 (51.9)	28 (52.8)	16 (48.5)	5 (55.6)	6 (54.5)	0.97
Rectum	51 (48.1)	25 (47.2)	17 (51.5)	4 (44.1)	5 (45.5)	
Timing of hepatic metastases						
Synchronous	44(41.5)	19 (35.8)	20 (60.6)	2 (22.2)	3 (27.3)	0.05
Metachronous	62 (58.5)	34 (64.2)	13 (39.4)	7 (77.8)	8 (72.7)	
Surgery type						
Minor (1-2 segment)	81 (76.4)	42 (79.2)	24(72.7)	9 (100)	6 (54.5)	0.10
Major (≥ 3 segment or hemihepatectomy)	25 (23.6)	11 (20.8)	9 (27.3)	0 (0)	5 (45.5)	
No. of hepatic CRM						
Single	61 (57.5)	34 (64.2)	17 (51.5)	6 (66.7)	4 (36.4)	0.29
Multiple	45 (42.5)	19 (35.8)	16 (48.5)	3 (33.3)	7 (63.6)	
Largest hepatic CRM tumor size, cm	10.4	4.87	4.55	4.73	4.05	0.87
Median estimated blood loss, mL	200	400	350	600	300	0.90
Duration of chemotherapy, wk (median)	4	0	4.8	4.1	0	< 0.0001
Postoperative complication						
Yes	20 (18.9)	7 (13.2)	9 (27.3)	0 (0)	4 (36.4)	0.07
No	86 (81.1)	46 (86.8)	24 (72.7)	9 (100)	7 (63.6)	

CRM: Colorectal metastases; HAI: Hepatic artery infusion.

Table 3 Liver injury characteristics stratified by preoperative therapy *n* (%)

Regimen	Liver toxicity (*n* = 51)			Steatosis > 30% (*n* = 16)			Sinusoidal dilation (*n* =31)			Steatohepatitis (*n* = 20)		
	Yes	No	[1]*P* value	Yes	No	[1]*P* value	Yes	No	[1]*P* value	Yes	No	[1]*P* value
No CTx	19 (35.8)	34 (64.2)		5 (9.4)	48 (90.6)		11 (20.8)	42 (79.2)		6 (11.3)	47 (88.7)	
Oxaliplatin	19 (57.6)	14 (42.4)	0.04	5 (15.2)	28 (84.8)	NS	14 (42.4)	19 (57.6)	0.03	7 (21.2)	26 (78.8)	NS
Irinotecan	5 (55.6)	4 (44.4)	NS	2 (22.2)	7 (77.8)	NS	1 (11.1)	8 (88.9)	NS	3 (33.3)	6 (66.7)	0.08
HAI	8 (72.7)	3 (27.3)	0.02	4 (36.4)	7 (63.6)	0.02	5 (45.5)	6 (54.5)	0.08	4 (36.4)	7 (63.6)	0.03

[1]Presence of liver injury characteristic; each chemotherapy group *vs* no chemotherapy. CTx: Chemotherapy; NS: Not significant; HAI: Hepatic artery infusion.

value was not statistically significant. Specifically, HAI was also associated with more steatosis, sinusoidal dilation and steatohepatitis than no preoperative treatment. HAI was associated with steatosis and steatohepatitis compared with non treatment before surgery (36.4% *vs* 9.4%, $P = 0.02$; 36.4% *vs* 11.3%, $P = 0.03$, respectively) and patients receiving HAI tended to have a higher likelihood of sinusoidal dilation compared with no chemotherapy (45.5% *vs* 20.8%, $P = 0.08$), although the *P* value was not statistically significant.

There were three patients who died within 90 d of surgery, with a perioperative mortality rate of 2.8%. Of those three deaths, one was due to renal failure, one was associated with an abdominal infection and a bile leak and another from acute respiratory distress syndrome (ARDS). There were two deaths among the preoperative chemotherapy (1.8%), all from oxaliplatin preoperative treatment, while another death occurred in the HAI arm (0.9%). There is no association between preoperative chemotherapy and the risk of perioperative mortality ($P = 0.1$). Patients with oxaliplatin ($n = 33$) tended to have a higher risk of death (6.1%) *vs* no preoperative treatment (0%), although the *P* value was not statistically significant ($P = 0.07$). There were 2 deaths (3.9%) in 51 patients with hepatic injury (one death was associated with an abdominal infection and a bile leak, another from ARDS) compared with one death (1.8%) in 55 patients without hepatic injury (one from renal failure).

In our study, there were seven patients with concomitant hepatitis before surgery, six with hepatitis B virus infection and one with hepatitis C virus infection. Two of these received neoadjuvant chemotherapy. However no further liver injury or complication was observed in those two patients.

DISCUSSION

Currently, chemotherapy has been commonly used as a part of an integrated multimodality approach to CRM and sometimes as the first treatment choice. Recently, an increasing number of reports have shown that the administration of preoperative chemotherapy can be associ-

ated with pathological changes in liver parenchyma[12-16]. However, the question remains whether these hepatic injuries have any clinical significance.

In the current study, we performed a retrospective analysis on the result of the use of preoperative treatment, including chemotherapy and HAI, for any impact on pathological liver injury and on clinical outcome, including postoperative complication and mortality.

Our study results show that preoperative treatment with oxaliplatin was significantly associated with a greater likelihood of sinusoidal dilation compared with no chemotherapy (42.4% *vs* 20.8%, $P = 0.03$), which is consistent with other recently published studies[15,20-22].

Interestingly, we observed that the incidence of sinusoidal dilation with oxaliplatin was 42.4%, relatively higher than Vauthey *et al*[16] (18.9%) and Pawlik *et al*[22] reported (9.6%). The reason for the different prevalence of sinusoidal dilation is probably multifactorial. Although progress has been made in this area, cohesive guidelines have yet to be proposed and consensus is lacking on a uniform set of pathological terminology to define chemotherapy-associated liver injury. The subjective variability between expert pathologists can lead to a different incidence rate of pathological changes in liver parenchyma. That is why we decided to have only one pathologist with hepatobiliary expertise assess the degree of liver injury and follow Vauthey's[16] strict definition.

Until now, only a few studies have been able to connect a given chemotherapeutic agent with a specific histopathological injury and a meaningful adverse outcome[16]. In our study, preoperative oxaliplatin was not significantly associated with an increase risk of postoperative complication (27.3% *vs* 13.2%, $P = 0.1$). Similar results were observed in other studies[22-24], indicating that preoperative oxaliplatin had no impact on postoperative morbidity or mortality.

Among previous reports, only Vauthey *et al* linked irinotecan-based chemotherapy with steatohepatitis and increased 90 d postoperative mortality[12-16]; 34 (8.4%) patients had steatohepatitis as defined by the nonalcoholic steatohepatitis score. Irinotecan was associated with steatohepatitis (20.2% incidence in the irinotecan group *vs* 4.4% in the non-chemotherapy group, $P = 0.0001$) and patients with steatohepatitis had an increased 90 d mortality rate compared with patients who did have steatohepatitis. In our study, steatohepatitis (Kleiner score $\geqslant 4$) was observed in 20 patients (18.8%), a higher rate than that Vauthey reported (20.2%). However, no postoperative complication or mortality was observed in patients with irinotecan treatment. We need to closely monitor the patient's status when we use irinotecan before surgery due to a relatively high steatohepatitis incidence rate, although data is not sufficient at present.

HAI has been used extensively in the palliative treatment of unresectable hepatocellular carcinoma. It was observed in several studies that it could improve quality of life, symptomatic control and survival time as a local therapy for CRM[25-28]. HAI is increasingly used in China as a palliative treatment of unresectable CRM as it may increase the possibility of surgery and can be used when surgery is not possible or not successful. However, less attention has been paid to the hepatic histological injures and perioperative complications after HAI, since it is commonly excluded from preoperative studies which observe the impact on hepatic histology and its outcomes for CRM. Until now, limited studies have explored whether HAI can affect the remaining liver for CRM and determine whether it can be used before surgery to improve postoperative recovery. Pulitanò *et al*[29] reported that postoperative morbidity rate were comparable between the HAI group and surgery alone group (14% *vs* 14%). He concluded that HAI of fluorodeoxyuridine does not negatively affect the outcome of subsequent liver resection. However, his article did not evaluate the hepatic pathological changes. In our study, we observed that HAI was associated with a higher risk of steatosis, sinusoidal dilation and steatohepatitis compared with non treatment before surgery. In addition, patients who received HAI tended to have more postoperative morbidity and mortality; those data alerted us to be more careful about its adverse impact on hepatic histology, despite a limited small sample size.

Discussion about the optimum interval between chemotherapy and hepatectomy has been based on the assumption that hepatic side effects of chemotherapy are time-related and reversible. Kopetz *et al*[30] reviewed the data and stated that a limited course of chemotherapy, with an interval of at least 5 wk, might minimize the incidence of surgical complications. Although the optimal timing of hepatic resection after completion of chemotherapy varies among institutions, a consensus is evolving for a minimum interval of 4 wk to allow the liver to recover, in the hope of reducing morbidity and mortality. In our study, almost all recruited patients received hepatic resection after completion of chemotherapy with an interval of 4-6 wk. Based on the clinical practice in our cancer center, the preoperative complication rate is observed at 13.2%, comparable with other reported papers[29].

Given this, the use of preoperative chemotherapy and HAI may need to be more carefully monitored and the choice of regimen and duration of treatment tailored to the particular individual's situation. Future investigations will be needed to clarify the pathogenesis and molecular pathways underlying the cause of chemotherapy-associated liver injury and its relationship to other known pathways. In addition, only through a thorough understanding of the patient's status and the patient's liver condition prior to administration of systemic chemotherapy can potentially confounding variables be accounted for and the true impact of systemic chemotherapy on the liver be determined[22].

Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, the preoperative oxaliplatin had no significant impact on perioperative outcomes. HAI can cause pathological changes and tends to increase perioperative morbidity and mortality.

COMMENTS

Background

Colorectal cancer (CRC) is one of the most common causes of cancer death in the Western world, ranking second in Europe and third in the United States. The incidence of CRC in China is lower than that in the West, but has increased in recent years and become a substantial burden in China. Some studies have reported changes in the characteristics of colorectal cancers in China.

Research frontiers

Preoperative chemotherapy before resection of hepatic colorectal metastases may cause hepatic injury and affect the postoperative outcome. The objective of this study was to assess the effects of preoperative treatment on the hepatic histology of non-tumoral liver and the postoperative outcome.

Terminology

Preoperative oxaliplatin was associated with sinusoidal dilation compared with surgery alone. However, preoperative oxaliplatin had no significant impact on perioperative outcomes. Hepatic artery infusion can cause pathological changes and tends to increase perioperative morbidity and mortality.

Peer review

The data presented in this paper is very interesting, especially the references about the impact of the duration of chemotherapy and the effect of hepatic artery infusion on the liver parenchyma. It is worthy of being published.

REFERENCES

1 **Jemal A**, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. *CA Cancer J Clin* 2005; **55**: 10-30 [PMID: 15661684 DOI: 10.3322/canjclin.55.1.10]

2 **Jemal A**, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. *CA Cancer J Clin* 2006; **56**: 106-130 [PMID: 16514137 DOI: 10.3322/canjclin.56.2.106]

3 **Cao KJ**, Ma GS, Liu YL, Wan DS. [Incidence of colorectal cancer in Guangzhou City from 2000 to 2002]. *Ai Zheng* 2009; **28**: 441-444 [PMID: 19622309]

4 **Zhang S**, Cui Y, Weng Z, Gong X, Chen M, Zhong B. Changes on the disease pattern of primary colorectal cancers in Southern China: a retrospective study of 20 years. *Int J Colorectal Dis* 2009; **24**: 943-949 [PMID: 19424708 DOI: 10.1007/s00384-009-0726-y]

5 **Jiang SX**, Wang XS, Geng CH, Wang GY. Altering trend of clinical characteristics of colorectal cancer: a report of 3,607 cases. *Ai Zheng* 2009; **28**: 54-56 [PMID: 19448417]

6 **Stangl R**, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; **343**: 1405-1410 [PMID: 7515134 DOI: 10.1016/S0140-6736(94)92529-1]

7 **Leonard GD**, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005; **23**: 2038-2048 [PMID: 15774795 DOI: 10.1200/JCO.2005.00.349]

8 **Nordlinger B,** Jaeck D, Guiguet M, Vaillant JC, Balladur P, Schaal JC. Surgical reaction of hepatic metastases. Multicentre retrospective study by the French Association of Surgery. In: Nordlinger B, Jack D editor. Treatment of hepatic metastases of colorectal cancer. Paris: Springer-Verlag, 1992: 129-156 [DOI: 10.1007/978-3-642-51873-7_12]

9 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-318; discussion 318-321 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

10 **Scheele J**. Hepatectomy for liver metastases. *Br J Surg* 1993; **80**: 274-276 [PMID: 8472130 DOI: 10.1002/bjs.1800800302]

11 **Adam R**, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, Kunstlinger F, Levi F, Bismuth F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001; **8**: 347-353 [PMID: 11352309 DOI: 10.1007/s10434-001-0347-3]

12 **Rubbia-Brandt L**, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; **15**: 460-466 [PMID: 14998849]

13 **Kooby DA**, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS, DeMatteo RP, D'Angelica M, Blumgart LH, Jarnagin WR. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg* 2003; **7**: 1034-1044 [PMID: 14675713]

14 **Fernandez FG**, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg* 2005; **200**: 845-853 [PMID: 15922194 DOI: 10.1016/j.jamcollsurg.2005.01.024]

15 **Karoui M**, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006; **243**: 1-7 [PMID: 16371728 DOI: 10.1097/01.sla.0000193603.26265.c3]

16 **Vauthey JN**, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; **24**: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]

17 **Zorzi D**, Mullen JT, Abdalla EK, Pawlik TM, Andres A, Muratore A, Curley SA, Mentha G, Capussotti L, Vauthey JN. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. *J Gastrointest Surg* 2006; **10**: 86-94 [PMID: 16368496 DOI: 10.1016/j.gassur.2005.07.022]

18 **Pang YY**. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2: 333-39. *HPB* (Oxford) 2002; **4**: 99; author reply 99-100 [PMID: 18332933]

19 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461]

20 **Nakano H**, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P, Jaeck D. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008; **247**: 118-124 [PMID: 18156931 DOI: 10.1097/SLA.0b013e31815774de]

21 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016 [PMID: 18358928]

22 **Pawlik TM**, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 2007; **11**: 860-868 [PMID: 17492335 DOI: 10.1007/s11605-007-0149-4]

23 **Sahajpal A**, Vollmer CM, Dixon E, Chan EK, Wei A, Cattral MS, Taylor BR, Grant DR, Greig PD, Gallinger S. Chemotherapy for colorectal cancer prior to liver resection for colorectal cancer hepatic metastases does not adversely affect peri-operative outcomes. *J Surg Oncol* 2007; **95**: 22-27 [PMID: 17066435 DOI: 10.1002/jso.20632]

24 **Ryan P**, Nanji S, Pollett A, Moore M, Moulton CA, Gallinger S, Guindi M. Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantitative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. *Am J Surg Pathol* 2010; **34**: 784-791 [PMID: 20421779 DOI: 10.1097/PAS.0b013e3181dc242c]

25 **Wasser K**, Giebel F, Fischbach R, Tesch H, Landwehr P. [Transarterial chemoembolization of liver metastases of colorectal carcinoma using degradable starch microspheres (Spherex): personal investigations and review of the literature]. *Radiologe* 2005; **45**: 633-643 [PMID: 15316615 DOI: 10.1007/s00117-004-1061-5]

26 **Popov I**, Lavrnić S, Jelić S, Jezdić S, Jasović A. Chemoembolization for liver metastases from colorectal carcinoma: risk or a benefit. *Neoplasma* 2002; **49**: 43-48 [PMID: 12044059]

27 **Müller H**, Nakchbandi V, Chatzisavvidis I, von Voigt C. Repetitive chemoembolization with melphalan plus intra-arterial immuno-chemotherapy within 5-fluorouracil and granulocyte-macrophage colony-stimulating factor (GM-CSF) as effective first- and second-line treatment of disseminated colorectal liver metastases. *Hepatogastroenterology* 2003; **50**: 1919-1926 [PMID: 14696433]

28 **Barber FD**, Mavligit G, Kurzrock R. Hepatic arterial infusion chemotherapy for metastatic colorectal cancer: a concise overview. *Cancer Treat Rev* 2004; **30**: 425-436 [PMID: 15245775 DOI: 10.1016/j.ctrv.2004.04.002]

29 **Pulitanò C**, Arru M, Catena M, Guzzetti E, Vitali G, Ronzoni M, Venturini M, Villa E, Ferla G, Aldrighetti L. Results of preoperative hepatic arterial infusion chemotherapy in patients undergoing liver resection for colorectal liver metastases. *Ann Surg Oncol* 2008; **15**: 1661-1669 [PMID: 18373123 DOI: 10.1245/s10434-008-9882-5]

30 **Kopetz S**, Vauthey JN. Perioperative chemotherapy for resectable hepatic metastases. *Lancet* 2008; **371**: 963-965 [PMID: 18358910 DOI: 10.1016/S0140-6736(08)60429-8]

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CASE REPORT

Clostridium difficile enteritis: A report of two cases and systematic literature review

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Abstract

Clostridium difficile (*C. difficile*) is the most common cause of healthcare associated infectious diarrhea. In the last decade, the incidence of *C. difficile* infection has increased dramatically. The virulence of *C. difficile* has also increased recently with toxigenic strains developing. *C. difficile* is generally a disease of the colon and presents with abdominal pain and diarrhea due to colitis. However, *C. difficile* enteritis has been reported rarely. The initial reports suggested mortality rates as high as 66%. The incidence of *C. difficile* enteritis appears to be increasing in parallel to the increase in colonic infections. We present two cases of patients who had otherwise uneventful abdominal surgery but subsequently developed *C. difficile* enteritis. Our literature review demonstrates 81 prior cases of *C. difficile* enteritis described in case reports. The mortality of the disease remains high at approximately 25%. Early recognition and intervention may reduce the high mortality associated with this disease process.

Key words: Clostridium difficile; Enteritits; Antibiotics; Colorectal surgery; Nosocomial infection

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INTRODUCTION

Clostridium difficile (*C. difficile*) is a common nosocomial infection caused by a gram-negative spore forming organism that most commonly leads to pseudomembranous colitis[1,2]. The incidence of *C. difficile* infection has been increasing rapidly since the early 2000s[2,3]. The rate of *C. difficile* infection nearly tripled between 1996 and 2005[2]. The number of severe cases of *C. difficile* infection is also rising; the number of fatal cases in England rose from approximately 500 in 1999 to nearly 3400 in 2006[2]. The increasing severity of disease may be due to a rise in an epidemic strain, NAP1/BI/027, which produces toxin A and B in significantly greater quantity compared to the normally occurring strain. *C. difficile* resides in the colon and risk factors for infection, such as antibiotic use, are generally those that alter normal colonic flora. However, we present two cases of patients diagnosed and treated with *C. difficile* enteritis. Due to the rare nature of this disease we reviewed the literature on the subject and present data to suggest increasing recognition of this manifestation of *C. difficile*.

CASE REPORT

Case 1

The first patient is a 54-year-old Caucasian male with ulcerative colitis who underwent a total proctocolectomy with end ileostomy in 1997. He developed a parastomal

hernia that was becoming increasingly symptomatic. Following a discussion with the patient regarding the risks and benefits of parastomal hernia repair, he underwent an exploratory laparotomy with enterolysis, parastomal hernia repair and re-siting of the ileostomy. The hernia defect was repaired primarily with a biologic mesh underlay (Alloderm, Lifecell®). He received one preoperative dose of cefoxitin; consistent with preoperative antibiotic guidelines. The operation was uneventful. His postoperative course was uncomplicated; on postoperative day 4 he was tolerating a regular diet and had normal ileostomy output. He was subsequently discharged home.

Twenty-four hours later, he returned to the hospital emergency department with complaints of abdominal pain and feculent vomiting. Vital signs on arrival were notable for a temperature of 38.5 ℃, heart rate of 130 beats per minute and blood pressure of 150/90 mmHg. On physical exam his abdomen was diffusely tender to palpation without peritoneal signs. The ileostomy was viable and there was gas and a small amount of fluid noted in the ostomy bag. A nasogastric tube was placed and returned 1600 mL of feculent effluent.

Laboratory examination revealed a white blood cell count of 5400 cells/mm^3, hemoglobin of 16 g/dL, and 192 000 platelets/mm^3 and a serum lactate of 2.1 mg/dL. An abdominal and pelvic computed tomography (CT) scan obtained in the emergency department revealed mildly dilated, fluid filled small bowel without a transition point. There was a small amount of free fluid and air which was consistent with the history of recent laparotomy. Blood cultures were obtained in the emergency department.

He was transferred to the intensive care unit for fluid resuscitation and started on broad-spectrum antibiotics. Serial abdominal exams were performed over the course of the next several hours, and he began to stabilize clinically. Notably, his tachycardia began to resolve and his urine output increased. Additionally, during this time, his ileostomy began to produce copious amounts of fluid and gas requiring frequent ostomy bag changes. The following day, his blood cultures returned positive for *Enterococcus* and his stool studies from his stoma output were positive for *C. difficile*.

Treatment for *C. difficile* was initiated with oral metronidazole but was subsequently changed to a combination of intravenous metronidazole and vancomycin enemas as the patient was not tolerating oral intake well. On hospital day 2, the antibiotic regimen used to treat the bacteremia was tailored to intravenous vancomycin alone based on sensitivity information. The patient improved with his antibiotic treatment and was transitioned to oral vancomycin for treatment of *C. difficile*. He was treated for a total of 14 d and he had complete resolution of his symptoms.

Case 2

The second case is a 48-year-old male patient with a history of diverticulitis who presented with left lower quadrant abdominal pain. His vital signs were normal on admission. A CT scan revealed inflammation of the sigmoid colon without evidence of a discrete fluid collection. The patient was initially started on intravenous antibiotics. However, approximately 24 h following admission, the patient developed worsening abdominal pain. His abdominal examination demonstrated worsening tenderness, with diffuse rebound and guarding. After discussion of operative risks he was taken to the operating room for exploration.

The sigmoid colon demonstrated only a focal area of perforation with moderate inflammation. A sigmoidectomy was performed with healthy proximal tissue and normal rectum. A primary anastomosis was performed using an EEA stapling device. A diverting ileostomy was performed to protect the anastomosis. The patient received 24 h of antibiotic treatment prior to operation which included three doses each of ciprofloxacin and metronidazole. Postoperatively, the patient developed an ileus which resolved on postoperative day 6. He was tolerating a diet following this. On postoperative day 8, the patient experienced significantly increased output from his ileostomy (greater than 2 L). A *C. Difficile* toxin sent from the ileostomy returned positive. The patient was started on intravenous metronidazole and improved. He was transitioned to oral medications upon discharge to complete a 14 d course.

Literature review

A systematic literature review was conducted by searching PubMed for the terms "enteritis" and "*Clostridium difficile*". One hundred and ninety-two citations were screened. One-hundred and fifty-eight were excluded based on review of title or abstract. Thirty-four citations were reviewed and the references of individual reports were hand searched to identify any missed reports. Data was extracted from individual case reports. All patients were symptomatic and tested positive for *C. difficile*. There were 34 reports identified from this search (Figure 1). We did not perform a meta-analysis due to the heterogeneity of the data and lack of randomized trials.

There were 81 cases of *C. difficile* enteritis found in the literature[4-37], with the addition of our cases, the total number of cases is now 83. Figure 2 illustrates that the number of cases has increased considerably in the last decade. There were 9 cases reported between the years 1980 and 2000. Since then there have been 73 cases reported. The mortality from the first 9 cases reported was 67% (6/9). The overall mortality of the 83 cases published is 23%. The average age of patients is 54 ± 2.44 years. Male patients constituted 53% of the cohort. Antibiotic use in the prior 4 wk was 71% and the incidence of inflammatory bowel disease was 41%. Twenty-one of 83 patients died resulting in a mortality rate of 23%.

DISCUSSION

C. difficile is the most common cause of health care-associated infectious diarrhea[3]. As first described, *C. difficile*

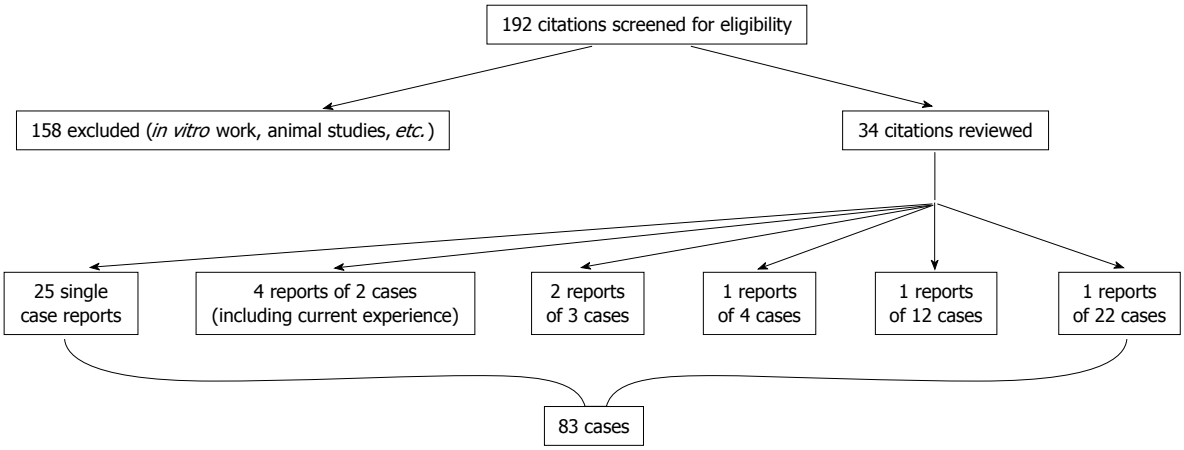

Figure 1 CONSORT diagram indicating the results of the systematic literature review. The results of the systematic review demonstrated 34 citations that met criteria for inclusion. There were a total of 83 patient-cases of *Clostridium difficile* enteritis identified.

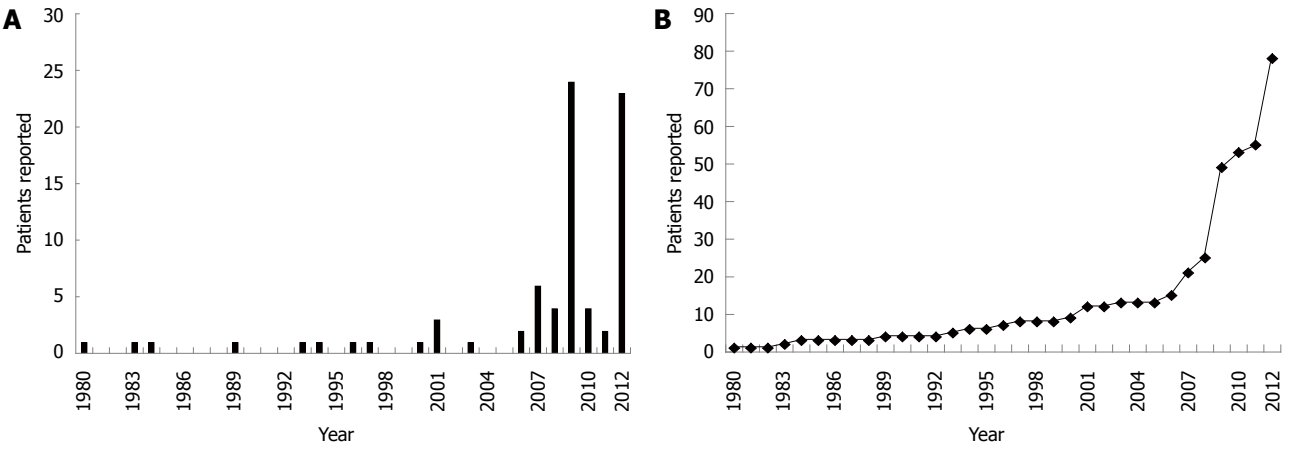

Figure 2 Number of cases has increased considerably in the last decade. A: The number of cases (patients) reported in the literature each year between 1980-2012; B: The cumulative number of cases over the same time period.

colitis was thought to be associated with the exclusive use of clindamycin administration[2]. Ironically, the bacteria that was difficult to grow (thus the *difficile*) is now increasing with dramatic incidence[2,38]. The increase in incidence is due, in part, to the highly virulent NAP1/BI/027 strain of *C. difficile*. In the United States, the frequency of *C. difficile* infection has doubled in the past 10 years[38]. The understanding of *C. difficile* and its pathophysiology has increased substantially over the past few decades. Severe *C. difficile* infection is being reported more frequently in patients not previously thought to be at high risk, including children[38,39]. It is possible that *C. difficile* enteritis is less dependent on alterations in colonic flora to develop. *C difficile* enteritis has previously been considered a rare disease. However, as highlighted in our review, the incidence of this also appears to be increasing.

Predisposing factors to *C. difficile* infection include prior antibiotic use; which is thought to alter the colonic flora, allowing *C. difficile* to proliferate. Many case reports, including ours, would suggest that previous antibiotic use is also associated with *C. difficile* enteritis. Lavallée *et al*[19] report that ten of twelve patients with ileal *C. difficile* had recent antibiotic administration (one did not have recent antibiotic use and one was not documented). Similarly, Lundeen *et al*[20] present 6 cases of *C. difficile* enteritis in which all 6 cases had recent antibiotic exposure. However, Tsiouris *et al*[30] report 22 cases in which the association with prior antibiotic use is less strong. Of the 22 patients in this series, only 22.7% demonstrated recent use of antibiotics. Based on our review, the association is still high, as 71% of patients had received antibiotics within 4 wk of presentation with *C. difficile* enteritis.

It is believed that gastric acid is a key mechanism of defense against ingested pathogens[1]. *C. difficile* has been identified as a pathogen in animals and has been identified in some food products[40]. Therefore, it is possible that transmission from ingested meats may occur[40]. Proton pump inhibitor (PPI) and H2-blockers are frequently used for gastric acid suppression. Acid suppressive therapy has been demonstrated to significantly increase the risk for *C. difficile* infection[1,41]. The patient in Case 1 was

treated preoperatively with a PPI for gastroesophageal reflux disease. Case 2 was not on outpatient therapy, but did receive a PPI postoperatively. This association is not entirely clear, however, as Lundeen *et al*[20] reported six cases, in which only one patient was on acid reducing therapy.

The pathophysiology of *C. difficile* enteritis is not well understood. Patients with an ileostomy may develop a metaplasia of the terminal end, creating an environment more similar to the colonic environment[42]. Additionally, changes in the intestinal flora have been noted after ileostomy[43]. Testore *et al*[44] isolated *C. difficile* from jejunum in asymptomatic human autopsy specimens. This supports the theory that small bowel may act as a reservoir. Kralovich *et al*[15] demonstrated *in vivo* that a patient with a jejunal-ileal bypass developed *C. difficile* infection in the defunctionalized limb. In addition to alterations in the host, changes in the pathogen may also be responsible for the development of *C. difficile* enteritis. Small bowel mucosa requires a higher concentrations of toxin for infection to occur[45]. In this case, the toxigenic NAP1/BI/027 strain may be more capable of causing small bowel infection. This is hypothetical at this point, but the increased recognition of *C. difficile* enteritis is compatible with the timing of the rise in NAP1/BI/027. This strain has been confirmed as the causative agent in one case of *C. difficile* enteritis[19]. We did not specifically test for NAP1/BI/027 strain and, therefore, cannot determine if this was a predisposing factor in our patients.

The diagnosis of *C. difficile* enteritis requires a high index of suspicion. As many patients may not initially be suspected of *C. difficile* infection, CT scan evidence may be useful. Wee *et al*[33] reviewed CT scan findings in four patients with *C. difficile* enteritis. They suggest that ascites and fluid-filled small bowel in the presence of mild mesenteric stranding could be considered consistent with *C. difficile* enteritis. Our patient in Case 1 demonstrated fluid filled loops of small bowel and a moderate amount of ascites. This was initially thought to be due to his recent surgery. However, these findings are consistent with the reported CT findings of small bowel *C. difficile*.

Treatment for *C. difficile* enteritis is generally similar to that for colonic infections. Oral metronidazole is considered standard first line therapy. However, Follmar *et al*[8] report the use of vancomycin for metronidazole resistant *C. difficile*. Severe *C. difficile* infection may be better treated with vancomycin[46,47]. In our patient, due to his ileus and his severe clinical status, we elected to use intravenous metronidazole and vancomycin enemas for his initial treatment.

It should be noted that our review is focused on case reports. There is no prospective data on the incidence of *C. difficile* enteritis. Therefore, it is not possible to know whether the apparent increase in cases is a true increase in incidence or if there is simply more reporting of the disease. However, even in the context of simply more reporting, the mortality remains high and increased recognition will still remain a priority.

The mortality of *C. difficile* enteritis has historically been considered very high as the initial 9 reports demonstrated a mortality of 66%. However, as the experience has steadily accumulated, the mortality rate appears to be decreasing. Our report of a mortality rate of 25.3% is lower than earlier reports, but remains substantial. This clinical entity is still rare and requires a high index of suspicion to initiate treatment early. As the use of antibiotics, immunosuppressive agents, and the age of the patient population will all continue to increase it is likely that *C. difficile* infections, including *C. difficile* enteritis will only continue to increase. Awareness of this process and efforts to determine the optimal treatment will continue to be necessary.

REFERENCES

1 **Dial S**, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**: 2989-2995 [PMID: 16414946 DOI: 10.1001/jama.294.23.2989]

2 **Kelly CP**, LaMont JT. Clostridium difficile--more difficult than ever. *N Engl J Med* 2008; **359**: 1932-1940 [PMID: 18971494 DOI: 10.1056/NEJMra0707500]

3 **Loo VG**, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Béliveau C, Oughton M, Brukner I, Dascal A. Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med* 2011; **365**: 1693-1703 [PMID: 22047560 DOI: 10.1056/NEJMoa1012413]

4 **Boland E**, Thompson JS. Fulminant Clostridium difficile enteritis after proctocolectomy and ileal pouch-anal anastamosis. *Gastroenterol Res Pract* 2008; **2008**: 985658 [PMID: 19197378 DOI: 10.1155/2008/985658]

5 **Causey MW**, Spencer MP, Steele SR. Clostridium difficile enteritis after colectomy. *Am Surg* 2009; **75**: 1203-1206 [PMID: 19999913]

6 **El Muhtaseb MS**, Apollos JK, Dreyer JS. Clostridium difficile enteritis: a cause for high ileostomy output. *ANZ J Surg* 2008; **78**: 416 [PMID: 18380751 DOI: 10.1111/j.1445-2197.2008.04494.x]

7 **Fleming F**, Khursigara N, O'Connell N, Darby S, Waldron D. Fulminant small bowel enteritis: a rare complication of Clostridium difficile-associated disease. *Inflamm Bowel Dis* 2009; **15**: 801-802 [PMID: 18942764 DOI: 10.1002/ibd.20758]

8 **Follmar KE**, Condron SA, Turner II, Nathan JD, Ludwig KA. Treatment of metronidazole-refractory Clostridium difficile enteritis with vancomycin. *Surg Infect (Larchmt)* 2008; **9**: 195-200 [PMID: 18426352 DOI: 10.1089/sur.2006.089]

9 **Freiler JF**, Durning SJ, Ender PT. Clostridium difficile small bowel enteritis occurring after total colectomy. *Clin Infect Dis* 2001; **33**: 1429-131; discussion 1432 [PMID: 11565085 DOI: 10.1086/322675]

10 **Gagandeep D**, Ira S. Clostridium difficile enteritis 9 years after total proctocolectomy: a rare case report. *Am J Gastroenterol* 2010; **105**: 962-963 [PMID: 20372147 DOI: 10.1038/ajg.2009.680]

11 **Hayetian FD**, Read TE, Brozovich M, Garvin RP, Caushaj PF. Ileal perforation secondary to Clostridium difficile enteritis: report of 2 cases. *Arch Surg* 2006; **141**: 97-99 [PMID: 16415419 DOI: 10.1001/archsurg.141.1.97]

12 **Holmer C**, Zurbuchen U, Siegmund B, Reichelt U, Buhr HJ, Ritz JP. Clostridium difficile infection of the small bowel--two case reports with a literature survey. *Int J Colorectal Dis*

2011; **26**: 245-251 [PMID: 20628882 DOI: 10.1007/s00384-010-1001-y]
13 **Jacobs A**, Barnard K, Fishel R, Gradon JD. Extracolonic manifestations of Clostridium difficile infections. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2001; **80**: 88-101 [PMID: 11307591 DOI: 10.1097/00005792-200103000-00002]
14 **Kim KA**, Wry P, Hughes E, Butcher J, Barbot D. Clostridium difficile small-bowel enteritis after total proctocolectomy: a rare but fatal, easily missed diagnosis. Report of a case. *Dis Colon Rectum* 2007; **50**: 920-923 [PMID: 17468989 DOI: 10.1007/s10350-006-0784-y]
15 **Kralovich KA**, Sacksner J, Karmy-Jones RA, Eggenberger JC. Pseudomembranous colitis with associated fulminant ileitis in the defunctionalized limb of a jejunal-ileal bypass. Report of a case. *Dis Colon Rectum* 1997; **40**: 622-624 [PMID: 9152196 DOI: 10.1007/bf02055391]
16 **Kuntz DP**, Shortsleeve MJ, Kantrowitz PA, Gauvin GP. Clostridium difficile enteritis. A cause of intramural gas. *Dig Dis Sci* 1993; **38**: 1942-1944 [PMID: 8404420 DOI: 10.1007/bf1296124]
17 **Kurtz LE**, Yang SS, Bank S. Clostridium difficile-associated small bowel enteritis after total proctocolectomy in a Crohn's disease patient. *J Clin Gastroenterol* 2010; **44**: 76-77 [PMID: 19593163 DOI: 10.1097/MCG.0b013e3181a7481b]
18 **LaMont JT**, Trnka YM. Therapeutic implications of Clostridium difficile toxin during relapse of chronic inflammatory bowel disease. *Lancet* 1980; **1**: 381-383 [PMID: 6101841 DOI: 10.1016/SO140-6736(80)90939-3]
19 **Lavallée C**, Laufer B, Pépin J, Mitchell A, Dubé S, Labbé AC. Fatal Clostridium difficile enteritis caused by the BI/NAP1/027 strain: a case series of ileal C. difficile infections. *Clin Microbiol Infect* 2009; **15**: 1093-1099 [PMID: 19681954 DOI: 10.1111/j.1469-0691.2009.03004.x]
20 **Lundeen SJ**, Otterson MF, Binion DG, Carman ET, Peppard WJ. Clostridium difficile enteritis: an early postoperative complication in inflammatory bowel disease patients after colectomy. *J Gastrointest Surg* 2007; **11**: 138-142 [PMID: 17390162 DOI: 10.1007/s11605-006-0022-x]
21 **Malkan AD**, Pimiento JM, Maloney SP, Palesty JA, Scholand SJ. Unusual manifestations of Clostridium difficile infection. *Surg Infect (Larchmt)* 2010; **11**: 333-337 [PMID: 19795991 DOI: 10.1089/sur.2008.099]
22 **Mann SD**, Pitt J, Springall RG, Thillainayagam AV. Clostridium difficile infection--an unusual cause of refractory pouchitis: report of a case. *Dis Colon Rectum* 2003; **46**: 267-270 [PMID: 12576902 DOI: 10.1097/01.DCR.0000049480.78184.AA]
23 **Miller DL**, Sedlack JD, Holt RW. Perforation complicating rifampin-associated pseudomembranous enteritis. *Arch Surg* 1989; **124**: 1082 [PMID: 2774912]
24 **Navaneethan U**, Giannella RA. Thinking beyond the colon-small bowel involvement in clostridium difficile infection. *Gut Pathog* 2009; **1**: 7 [PMID: 19338685 DOI: 10.1186/1757-4749-1-7]
25 **Peacock O**, Speake W, Shaw A, Goddard A. Clostridium difficile enteritis in a patient after total proctocolectomy. *BMJ Case Rep* 2009; **2009**: [PMID: 21686438 DOI: 10.1136/bcr.10.2008.1165]
26 **Shen B**, Remzi FH, Fazio VW. Fulminant Clostridium difficile-associated pouchitis with a fatal outcome. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 492-495 [PMID: 19654602 DOI: 10.1038/nrgastro.2009.105]
27 **Shortland JR**, Spencer RC, Williams JL. Pseudomembranous colitis associated with changes in an ileal conduit. *J Clin Pathol* 1983; **36**: 1184-1187 [PMID: 6619315 DOI: 10.1136/jcp.36.10.1184]
28 **Testore GP**, Nardi F, Babudieri S, Giuliano M, Di Rosa R, Panichi G. Isolation of Clostridium difficile from human jejunum: identification of a reservoir for disease? *J Clin Pathol* 1986; **39**: 861-862 [PMID: 3745477 DOI: 10.1136/jcp.39.8.861]
29 **Tjandra JJ**, Street A, Thomas RJ, Gibson R, Eng P, Cade J. Fatal Clostridium difficile infection of the small bowel after complex colorectal surgery. *ANZ J Surg* 2001; **71**: 500-503 [PMID: 11504300 DOI: 10.1046/j.1440-1622.2001.02083.x]
30 **Tsiouris A**, Neale JA, Reickert CA, Times M. Clostridium difficile of the ileum following total abdominal colectomy, with or without proctectomy: who is at risk? *Dis Colon Rectum* 2012; **55**: 424-428 [PMID: 22426266 DOI: 10.1097/DCR.0b013e31823f86a2]
31 **Tsutaoka B**, Hansen J, Johnson D, Holodniy M. Antibiotic-associated pseudomembranous enteritis due to Clostridium difficile. *Clin Infect Dis* 1994; **18**: 982-984 [PMID: 8086563 DOI: 10.1093/clinids/18.6.982]
32 **Vesoulis Z**, Williams G, Matthews B. Pseudomembranous enteritis after proctocolectomy: report of a case. *Dis Colon Rectum* 2000; **43**: 551-554 [PMID: 10789757 DOI: 10.1007/bf02237205]
33 **Wee B**, Poels JA, McCafferty IJ, Taniere P, Olliff J. A description of CT features of Clostridium difficile infection of the small bowel in four patients and a review of literature. *Br J Radiol* 2009; **82**: 890-895 [PMID: 19620176 DOI: 10.1259/bjr/57970083]
34 **Williams RN**, Hemingway D, Miller AS. Enteral Clostridium difficile, an emerging cause for high-output ileostomy. *J Clin Pathol* 2009; **62**: 951-953 [PMID: 19447832 DOI: 10.1136/jcp.2008.062901]
35 **Wood MJ**, Hyman N, Hebert JC, Blaszyk H. Catastrophic Clostridium difficile enteritis in a pelvic pouch patient: report of a case. *J Gastrointest Surg* 2008; **12**: 350-352 [PMID: 18071831 DOI: 10.1007/s11605-007-0440-4]
36 **Yafi FA**, Selvasekar CR, Cima RR. Clostridium difficile enteritis following total colectomy. *Tech Coloproctol* 2008; **12**: 73-74 [PMID: 18524025 DOI: 10.1007/s10151-008-0402-1]
37 **Yee HF**, Brown RS, Ostroff JW. Fatal Clostridium difficile enteritis after total abdominal colectomy. *J Clin Gastroenterol* 1996; **22**: 45-47 [PMID: 8776096 DOI: 10.1097/00004836-199601000-00013]
38 **Tschudin-Sutter S**, Widmer AF, Perl TM. Clostridium difficile: novel insights on an incessantly challenging disease. *Curr Opin Infect Dis* 2012; **25**: 405-411 [PMID: 22614522 DOI: 10.1097/QCO.0b013e32835533a2]
39 **Benson L**, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. *Infect Control Hosp Epidemiol* 2007; **28**: 1233-1235 [PMID: 17926272 DOI: 10.1086/520732]
40 **Songer JG**, Trinh HT, Killgore GE, Thompson AD, McDonald LC, Limbago BM. Clostridium difficile in retail meat products, USA, 2007. *Emerg Infect Dis* 2009; **15**: 819-821 [PMID: 19402980 DOI: 10.3201/eid1505.081071]
41 **Howell MD**, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, Talmor D. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. *Arch Intern Med* 2010; **170**: 784-790 [PMID: 20458086 DOI: 10.1001/archinternmed.2010.89]
42 **Apel R**, Cohen Z, Andrews CW, McLeod R, Steinhart H, Odze RD. Prospective evaluation of early morphological changes in pelvic ileal pouches. *Gastroenterology* 1994; **107**: 435-443 [PMID: 8039620]
43 **Neut C**, Bulois P, Desreumaux P, Membré JM, Lederman E, Gambiez L, Cortot A, Quandalle P, van Kruiningen H, Colombel JF. Changes in the bacterial flora of the neoterminal ileum after ileocolonic resection for Crohn's disease. *Am J Gastroenterol* 2002; **97**: 939-946 [PMID: 12003430 DOI: 10.1111/j.1572-0241.2002.05613.x]
44 **Testore GP**, Pantosti A, Cerquetti M, Babudieri S, Panichi G, Gianfrilli PM. Evidence for cross-infection in an outbreak of Clostridium difficile-associated diarrhoea in a surgical

unit. *J Med Microbiol* 1988; **26**: 125-128 [PMID: 3385765 DOI: 10.1099/00222615-26-2-125]
45 **Triadafilopoulos G**, Pothoulakis C, O'Brien MJ, LaMont JT. Differential effects of Clostridium difficile toxins A and B on rabbit ileum. *Gastroenterology* 1987; **93**: 273-279 [PMID: 3596162]
46 **Cocanour CS**. Best strategies in recurrent or persistent Clostridium difficile infection. *Surg Infect* (Larchmt) 2011; **12**: 235-239 [PMID: 21767157 DOI: 10.1089/sur.2010.080]
47 **Zar FA**, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; **45**: 302-307 [PMID: 17599306 DOI: 10.1086/519265]

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CASE REPORT

Recurrent intestinal volvulus in midgut malrotation causing acute bowel obstruction: A case report

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Abstract

Intestinal malrotation occurs when there is a disruption in the normal embryological development of the bowel. The majority of patients present with clinical features in childhood, though rarely a first presentation can take place in adulthood. Recurrent bowel obstruction in patients with previous abdominal operation for midgut malrotation is mostly due to adhesions but very few reported cases have been due to recurrent volvulus. We present the case of a 22-year-old gentleman who had laparotomy in childhood for small bowel volvulus and then presented with acute bowel obstruction. Preoperative computerised tomography scan showed small bowel obstruction and features in keeping with midgut malrotation. Emergency laparotomy findings confirmed midgut malrotation with absent appendix, abnormal location of caecum, ascending colon and small bowel. In addition, there were small bowel volvulus and a segment of terminal ileal stricture. Limited right hemicolectomy was performed with excellent postoperative recovery. This case is presented to illustrate a rare occurrence and raise an awareness of the possibility of dreadful recurrent volvulus even several years following an initial Ladd's procedure for midgut malrotation. Therefore, one will need to exercise a high index of suspicion and this becomes very crucial in order to ensure prompt surgical intervention and thereby preventing an attendant bowel ischaemia with its associated high fatality.

Key words: Gut volvulus; Intestinal malrotation; Acute bowel obstruction; Computerised tomography scan; Laparotomy

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INTRODUCTION

Intestinal malrotation occurs when there is a disruption in the normal embryological development of the bowel rotation, elongation and fixation. Normal developmental gut rotation takes place around the superior mesenteric artery (SMA) which supplies the midgut. Disturbance of this process will lead to incomplete or non-rotation of the foetal midgut. This condition affects approximately 1 in 500 live births with the vast majority of the associated complications presenting in the first month of life when its diagnosis is made[1-3]. It has been reported that well over 90% of the affected individuals manifest by the time of their first birthday[1-5].

The diagnosis of midgut malrotation is rarely reported in adults[2,4-9]. A small proportion of the cases go undetected until adulthood when they are incidentally diagnosed in the course of radiological investigations or operative interventions for acute bowel obstruction or other unrelated conditions[3-6]. There is even a lesser

group of patients presenting later in life with intermittent non-specific acute or chronic symptoms where the diagnosis is particularly difficult to make and the condition can go on for life undetected[2,5-9].

This is a report of a young adult who previously underwent a laparotomy three weeks of age for bowel volvulus and represented later with acute small bowel obstruction due to recurrent volvulus in the setting of midgut malrotation. This unique case is reported to illustrate a rare occurrence of recurrent volvulus following Ladd's procedure for midgut malrotation. Therefore, a high index of suspicion is required for early diagnosis and prompt surgical intervention in order to prevent the risk of bowel gangrene and its associated high fatality.

CASE REPORT

A 22-year-old gentleman presented with three days history of an acute onset central abdominal pain, progressive distension and vomiting. Patient has been experiencing intermittent abdominal pain for weeks and erratic bowel habit with scanty pellet-like stool prior to presentation. He had presented 2 wk earlier and underwent an emergency left inguinal hernia repair which was misdiagnosed as the cause of the intermittent abdominal pain. There was a background history of laparotomy for "twisted" bowel when he was 3-wk-old.

Physical examination at this presentation showed dehydration, distended abdomen with tenderness around the umbilicus. There was no peritonitis and bowel sounds were high pitched and hyperactive. Rectum was empty.

Blood tests were unremarkable with normal parameters for full blood count, urea and electrolytes, liver function tests, arterial blood gases, C-reactive protein and lactate. The abdominal radiograph showed features of a small bowel obstruction. This was subsequently confirmed on the abdominal computerised tomography (CT) scan. The caecum was located to the upper left quadrant with the large bowel on the left of the abdomen and most of the small bowel loops were on the right side (Figure 1A). There was failure of progress of the duodenum to the left side of the spines and aorta (Figure 1B). There was also a reversal of the relationship between the mesenteric artery and vein (Figure 1C). A diagnosis of adhesions causing bowel obstruction in the setting of midgut malrotation was made.

The patient was adequately resuscitated and underwent an emergency laparotomy and limited right hemicolectomy with ileocolic anastomosis. The findings at operation were consistent with midgut malrotation, with small bowel on the right side and pelvis, caecum and ascending colon on the left upper abdomen and the duodenal-jejunal flexure on the right side of the ascending colon. The appendix was absent presumably removed at the previous laparotomy. There were minimal intra-abdominal adhesions. The cause of obstruction was small bowel volvulus with dilated, congested but viable bowel and a segment of chronically thickened and strictured terminal ileum presumably the site of previous ileoileal

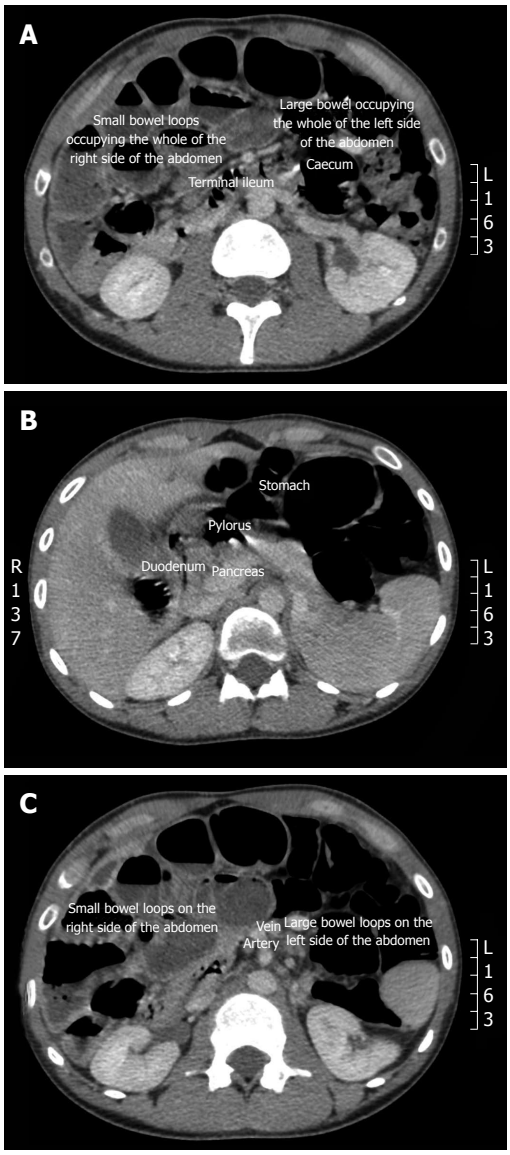

Figure 1 Computerised tomography scan. A: Abnormal location of the caecum and terminal ileum and most of the small bowel to the right side of the abdomen; B: Non-progression of the duodenum across the spines and aorta; C: Reversal of the relationship between mesenteric artery and vein.

anastomosis in childhood (Figure 2). The patient made a good recovery postoperatively and was discharged home a week after the operation. Follow up in the clinic showed no recurrence of symptoms up until 6 mo after surgery.

DISCUSSION

Midgut malrotation is a rare cause of intestinal obstruction in adult life and only few of such cases have been reported in the literature[2,4-11]. Recurrent intestinal obstruction is even rarer in adults who have been previously operated for gut malrotation and few of such cases have been reported. Features of intestinal obstruction in patients who have had previous laparotomy always raise the suspicion of adhesions as the aetiological factor. The other possible causes to consider are either postoperative

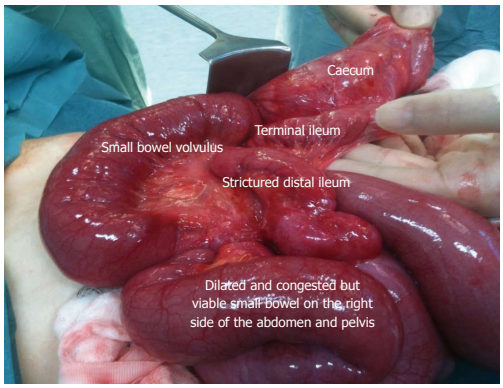

Figure 2 Intraoperative findings showing high riding left upper quadrant caecum, dilated congested but viable small bowel on the right of the abdomen. Terminal ileum entering the caecum on the right side.

midgut volvulus or internal herniation and few of the latter have been reported following laparoscopic appendicectomy, cholecystectomy and gastric banding operations[12-14]. The reason(s) for this rare phenomenon following laparoscopic operations is not well understood. Biko *et al*[15] in their retrospective review of obstructive symptoms in patients post Ladd's procedure showed that adhesive small bowel obstruction was more common than the most dreaded recurrent gut volvulus.

Midgut malrotation is rarely considered as an underlying diagnosis in adults and may present in various ways. Our patient had a history of abdominal surgery as a child for volvulus but there was no knowledge of the aetiological factor at the time of this presentation. He presented initially two weeks earlier with features of subacute obstruction and finding of a left inguinal hernia. He had a presumed diagnosis of an obstructed left inguinal hernia and underwent an emergency hernia operation. However, this treatment did not resolve his symptoms hence necessitating a representation with an acute bowel obstruction. The initial diagnosis of acute adhesive bowel obstruction was made on the background history of previous laparotomy he had as a 3-wk-old child. The clinical diagnosis of midgut malrotation in adolescents and adults is difficult because it is rarely considered on clinical grounds. Beside, many of these patients remain asymptomatic and majority of them are only discovered incidentally during investigations or laparotomy. Dietz *et al*[9] in a series of 10 adults with intestinal malrotation showed that 4 and 5 of them presented with acute and chronic bowel obstructive symptoms respectively and one patient had an acute abdomen due to appendicitis.

Recurrent volvulus as a cause of bowel obstruction following Ladd's operation for midgut malrotation is very rare both in children and adult life and very few of such cases have been reported in literature[15-21] (Table 1). Recurrent symptoms in such cases are usually considered to be due to adhesions and one may be inclined to adopt a non-operative approach. Fu *et al*[16] reported only two recurrences in a series of 12 adults treated for symptomatic malrotation with one of them requiring a reoperation and the other managed conservatively. It is

Table 1 Reported cases of recurrent intestinal volvulus following previous Ladd's procedure for midgut malrotation

Ref.	Year	No of cases	Diagnosis	Management of volvulus
Fu *et al*[16]	2007	3	2-recurrent volvulus 1-adhesive bowel obstruction	1-surgery 1-conservative treatment
Mazeh *et al*[17]	2007	1	Recurrent volvulus	Surgery
Alkan *et al*[18]	2007	1	Recurrent volvulus	Surgery
Tashjian *et al*[19]	2007	3	1-recurrent volvulus 1-adhesive bowel obstruction 1-closed loop obstruction	All had surgery
Panghaal *et al*[20]	2008	1	Recurrent volvulus	Surgery
El-Gohary *et al*[21]	2010	10	1-recurrent volvulus 9-adhesive bowel obstruction	Surgery
Biko *et al*[15]	2011	9	1-recurrent volvulus 8-adhesive bowel obstruction	Surgery
This case	2012	1	Recurrent volvulus	Surgery

believed that the increasing use of CT scan will enable one to make such diagnosis with certainty preoperatively as this has the overall advantage of detecting the abnormal location of the midgut as well as any other intra-abdominal anomalies. The finding of midgut malrotation should make one to suspect a possible diagnosis of intestinal volvulus which may require an early surgical intervention so as to prevent the most dreadful and life threatening bowel ischaemia and infarction.

The standard surgical intervention in patients with obstructive symptoms and gut malrotation is Ladd procedure which was originally described in paediatric population by Ladd[22]. This procedure consists of 4 elements including the division of Ladd's bands overlying the duodenum; widening of the narrowed root of the small bowel mesentery by mobilising the duodenum and division of the adhesions around the SMA to prevent further volvulus; counterclockwise detorsioning of the midgut volvulus if present and appendicectomy to prevent future diagnostic dilemma of an abnormally located inflamed appendix[22]. Most authors are of the opinion that Ladd's procedure is an adequate treatment for intestinal malrotation but various modifications of this operation have been reported. The full components of this procedure may not be required in the adult group to deal with the bowel obstruction[5,8,9,22]. One of the clear objectives of surgical management of midgut malrotation is to prevent recurrent volvulus and there are various techniques used to prevent such complication. This includes re-establishment of the normal gut anatomy by duodenopexy, caecopexy and suture fixation of the ascending colon to the right abdominal wall, in the retroperitoneal position[8,9]. There are reports of increasing use of laparoscopic approach to Ladd's operation in the literature[2,5,7] with excellent outcome.

It was difficult to ascertain the full details of the procedure(s) performed in our patient in childhood as the operation took place in a different hospital with una-

vailable medical records. Our best guess is that he may have had the standard Ladd's procedure at that age as the appendix and the classical Ladd's bands were absent at laparotomy. We presumed he may have also had a bowel resection for ischaemic bowel resulting from volvulus as evident by strictured distal ileum. There was no evidence that a caecopexy and/or fixation of the ascending colon to the right abdominal wall were performed. This patient had a recurrent small bowel volvulus and chronic stricture of the distal ileum causing acute bowel obstruction. Recurrent small bowel volvulus also may have been encouraged by the minimal adhesion formation following the laparotomy he had in childhood. He then underwent a limited right hemicolectomy and ileocolic anastomosis with an uneventful postoperative recovery.

In conclusion, midgut malrotation is rare in adult population but an important factor contributing to bowel obstruction in that group. The most dreadful and life threatening complication of intestinal malrotation both in children and adults is gut volvulus with possible ischaemic changes and associated high mortality. However, recurrent volvulus resulting from intestinal malrotation is uncommon after treatment with Ladd's procedure and only very few of such cases have been reported in the literature. Majority of recurrent bowel obstructive symptoms are due to adhesions from previous laparotomy. Therefore, one will need to exercise a high index of suspicion and an awareness of the possibility of recurrent volvulus even several years following an initial Ladd's procedure. This is crucial to ensure prompt surgical intervention in order to prevent attendant bowel ischaemia and a high fatality rate.

REFERENCES

1 **Torres AM**, Ziegler MM. Malrotation of the intestine. *World J Surg* 1993; **17**: 326-331 [PMID: 8337878 DOI: 10.1007/BF01658699]

2 **Matzke GM**, Moir CR, Dozois EJ. Laparoscopic ladd procedure for adult malrotation of the midgut with cocoon deformity: report of a case. *J Laparoendosc Adv Surg Tech A* 2003; **13**: 327-329 [PMID: 14617393 DOI: 10.1089/109264203769681736]

3 **Lee HC**, Pickard SS, Sridhar S, Dutta S. Intestinal malrotation and catastrophic volvulus in infancy. *J Emerg Med* 2012; **43**: e49-e51 [PMID: 22325550 DOI: 10.1016/j.jemermed.2011.06.135]

4 **Singh S**, Das A, Chawla AS, Arya SV, Chaggar J. A rare presentation of midgut malrotation as an acute intestinal obstruction in an adult: Two case reports and literature review. *Int J Surg Case Rep* 2013; **4**: 72-75 [PMID: 23123419 DOI: 10.1016/j.ijscr.2012.10.005]

5 **Emanuwa OF**, Ayantunde AA, Davies TW. Midgut malrotation first presenting as acute bowel obstruction in adulthood: a case report and literature review. *World J Emerg Surg* 2011; **6**: 22 [PMID: 21801417 DOI: 10.1186/1749-7922-6-22]

6 **Nath J**, Corder AP. Delayed presentation of familial intestinal malrotation with volvulus in two adult siblings. *Ann R Coll Surg Engl* 2012; **94**: e191-e192 [PMID: 22943318 DOI: 10.1308/003588412X13373405384819]

7 **Wanjari AK**, Deshmukh AJ, Tayde PS, Lonkar Y. Midgut malrotation with chronic abdominal pain. *N Am J Med Sci* 2012; **4**: 196-198 [PMID: 22536565 DOI: 10.4103/1947-2714.94950]

8 **Wang CA**, Welch CE. Anomalies of intestinal rotation in adolescents and adults. *Surgery* 1963; **54**: 839-855 [PMID: 14087118]

9 **Dietz DW**, Walsh RM, Grundfest-Broniatowski S, Lavery IC, Fazio VW, Vogt DP. Intestinal malrotation: a rare but important cause of bowel obstruction in adults. *Dis Colon Rectum* 2002; **45**: 1381-1386 [PMID: 12394439 DOI: 10.1007/s10350-004-6429-0]

10 **von Flüe M**, Herzog U, Ackermann C, Tondelli P, Harder F. Acute and chronic presentation of intestinal nonrotation in adults. *Dis Colon Rectum* 1994; **37**: 192-198 [PMID: 8306846 DOI: 10.1007/BF02047549]

11 **Rowsom JT**, Sullivan SN, Girvan DP. Midgut volvulus in the adult. A complication of intestinal malrotation. *J Clin Gastroenterol* 1987; **9**: 212-216 [PMID: 3571896 DOI: 10.1097/00004836-198704000-00021]

12 **Macedo M**, Velhote MC. Midgut volvulus after laparoscopic appendectomy. *Einstein* (Sao Paulo) 2012; **10**: 103-104 [PMID: 23045837]

13 **Vricella LA**, Barrett WL, Tannebaum IR. Intestinal obstruction from midgut volvulus after laparoscopic cholecystectomy. A report of an unusual complication. *Surg Endosc* 1999; **13**: 1234-1235 [PMID: 10594273]

14 **Arbell D**, Koplewitz B, Zamir G, Bala M. Midgut volvulus following laparoscopic gastric banding--a rare and dangerous situation. *J Laparoendosc Adv Surg Tech A* 2007; **17**: 321-323 [PMID: 17570779 DOI: 10.1089/lap.2006.0102]

15 **Biko DM**, Anupindi SA, Hanhan SB, Blinman T, Markowitz RI. Assessment of recurrent abdominal symptoms after Ladd procedure: clinical and radiographic correlation. *J Pediatr Surg* 2011; **46**: 1720-1725 [PMID: 21929980 DOI: 10.1016/j.jpedsurg.2011.03.018]

16 **Fu T**, Tong WD, He YJ, Wen YY, Luo DL, Liu BH. Surgical management of intestinal malrotation in adults. *World J Surg* 2007; **31**: 1797-803; discussion 1804-5 [PMID: 17457643 DOI: 10.1007/s00268-007-9018-2]

17 **Mazeh H**, Kaliner E, Udassin R. Three recurrent episodes of malrotation in an infant. *J Pediatr Surg* 2007; **42**: E1-E3 [PMID: 17448746 DOI: 10.1016/j.jpedsurg.2007.01.053]

18 **Alkan M**, Oguzkurt P, Alkan O, Ezer SS, Hiçsönmez A. A Rare but Serious Complication of Ladd's Procedure: Recurrent Midgut Volvulus. *Case Rep Gastroenterol* 2007; **1**: 130-134 [PMID: 21487558 DOI: 10.1159/000110601]

19 **Tashjian DB**, Weeks B, Brueckner M, Touloukian RJ. Outcomes after a Ladd procedure for intestinal malrotation with heterotaxia. *J Pediatr Surg* 2007; **42**: 528-531 [PMID: 17336193 DOI: 10.1016/j.jpedsurg.2006.10.060]

20 **Panghaal V**, Levin TL, Han B. Recurrent midgut volvulus following a Ladd procedure. *Pediatr Radiol* 2008; **38**: 471-472 [PMID: 18084753 DOI: 10.1007/s00247-007-0703-y]

21 **El-Gohary Y**, Alagtal M, Gillick J. Long-term complications following operative intervention for intestinal malrotation: a 10-year review. *Pediatr Surg Int* 2010; **26**: 203-206 [PMID: 19756654 DOI: 10.1007/s00383-009-2483-y]

22 **Ladd WE.** Surgical diseases of the alimentary tract in infants. N *Engl J Med* 1936; **215:** 705-708 [DOI: 10.1056/NEJM193610152151604]

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CASE REPORT

Perforated duodenal diverticulum, a rare complication of a common pathology: A seven-patient case series

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Abstract

Duodenal diverticula (DD) are frequently encountered and are usually asymptomatic, with an incidence at autopsy of 22%. Perforation of DD is a rare complication (around 160 cases reported) with potentially dramatic consequences. However, little evidence regarding its treatment is available in the literature. The aim of this study was to review our experience of perforated DD, with a focus on surgical management. Between January 2001 and June 2011, all perforated DD were retrospectively reviewed at a single centre. Seven cases (5 women and 2 men; median age: 72.4 years old, rang: 48-91 years) were found. The median American Society of Anesthesiologists' score in this population was 3 (range: 3-4). The perforation was located in the second portion of duodenum (D2) in six patients and in the third portion (D3) in one patient. Six of these patients were treated surgically: five patients underwent DD resection with direct closure and one was treated by surgical drainage and laparostomy. One patient was treated conservatively. One patient died and one patient presented a leak that was successfully treated conservatively. The median hospital stay was 21.1 d (range: 15-30 d). Perforated DD is an uncommon presentation of a common pathology. Diverticular excision with direct closure seems to offer the best chance of survival and was associated with a low morbidity, even in fragile patients.

Key words: Duodenal perforation; Duodenum; Duodenal diverticulum; Surgical management

Rossetti A, Buchs NC, Bucher P, Dominguez S, Morel P. Perforated duodenal diverticulum, a rare complication of a common pathology: A seven-patient case series. *World J Gastrointest Surg* 2013; 5(3): 47-50 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i3/47.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i3.47

INTRODUCTION

Duodenal diverticulum (DD) is common, with a reported prevalence of 22% at autopsy[1]. A similar incidence has been reported during endoscopicretrograde cholangiopancreatography (ERCP)[2,3]. The most frequent location is the second and third portions of the duodenum (D2-D3)[4].

Although, DD is rarely symptomatic and only 5% of patients present with symptoms due to the compression of neighbouring organs, cholestasis (in cases of periampullary diverticulum), haemorrhage, inflammation or perforation[4]. One hundred and sixty-two cases of perforated DD have been reported in the literature[5-8]. The supposed cause of perforation in 57% of cases is ischaemic processes due to distension related to food retention in the diverticula[9]. Other reported causes are ulcerations, enterocolitihs, blunt abdominal trauma and perforation due to the ERCP procedure[5,9-12].

However, diagnosis remains a challenge, with many potential differential diagnoses, including perforated duodenal ulcer. Helical computed tomography (CT) has emerged as a useful diagnostic tool and most centers now use CT routinely to confirm the diagnosis. Yet surgical exploration in unstable and septic patients is still considered mandatory, especially if the diagnosis is not clear[13,14].

The appropriate surgical management remains under debate. A surgical approach is usually advocated. However, some groups[5,14,15] have reported using a more conservative approach, and demonstrated that non-operative management is a safe and practical alternative to surgery in selected patients. The aim of this study was to review our 11-year experience with perforated DD at a single centre with a special focus on surgical management.

CASE REPORT

Between January 2001 and June 2011, all perforated DD were retrospectively reviewed at a single center. Only non-traumatic cases were included. Iatrogenic perforations (*e.g.* during endoscopy) were excluded from the study. For all the analyzed patients a CT-scan was performed at the admission. Seven cases (five women and two men; median age: 72.4 years old, range: 48-91 years) were found. The median American Society of Anesthesiologists' (ASA) score in this population was 3 (range: 3-4). Six cases were treated surgically and one with a naso-gastric tube and antibiotics (Taylor's approach for upper digestive perforation).

We report herein a series of seven cases of spontaneous DD perforation (Table 1). The clinical presentation was abdominal pain in six cases and bilateral basithoracic pain in one case. Of note, only one patient was admitted with severe septic shock. All the patients presented elevated leucocyte count and C-reactive protein. Diagnosis was performed by CT scans in 42.8% (3 out of 7) of the cases (Figure 1). Diagnosis of the other cases was made intra-operatively. Six patients underwent surgery (85.7%). Of these, five cases had an ASA score of 3 and one an ASA score of 4. The perforated DD was located at the D2 level in six cases (85.7%) (Figure 2A and B) and at the D3 level in one case. All the patients received endovenous antibiotics therapy for 10 d (ceftriaxone and metronidazole). In five cases surgical treatment (Table 2) involved resection of the DD and direct duodenal suture. A nutritional jejunostomy was also performed in three cases.

A transpapillary bilio-duodenal drain was used in the patient with a D3 perforation due to the proximity of Vater's papilla. Only one patient presented with septic shock, and at laparotomy, a damage control approach was chosen (drainage and laparostomy) given the instability of the patient, and the important bowel edema that did not allowed to close the abdominal wall.

The non-surgically treated case was treated with antibiotics and a naso-gastric tube because presented with only bilateral basithoracic pain, and a diagnosis of a cover DD perforation was performed on CT scan. An image control (Upper passage opacification Rx with gastrographine®) was performed after 7 d after the oral intake. In terms of outcome, a suture leak occurred in one patient at post-operative day-5; this leak did not require surgery and was conservatively treated with success (nasogastric tube and endovenous antibiotics). One patient died (mortality: 14.3%) after a cardiac complication-cardiac failure. This patient was admitted in a critical condition with severe septic shock and the preferred surgical treatment was damage control surgery. Oral intake was restored for all the patients on average seven days after the operation.

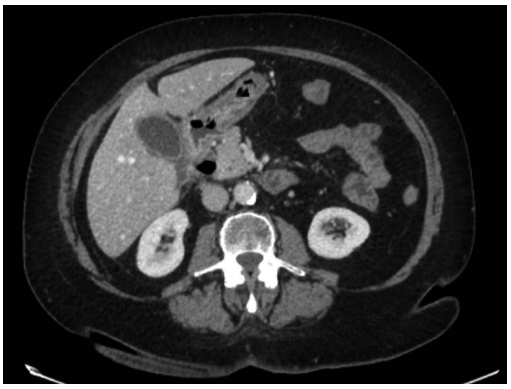

Figure 1 Computed tomography scan of case 5 showing a perforated duodenal diverticula.

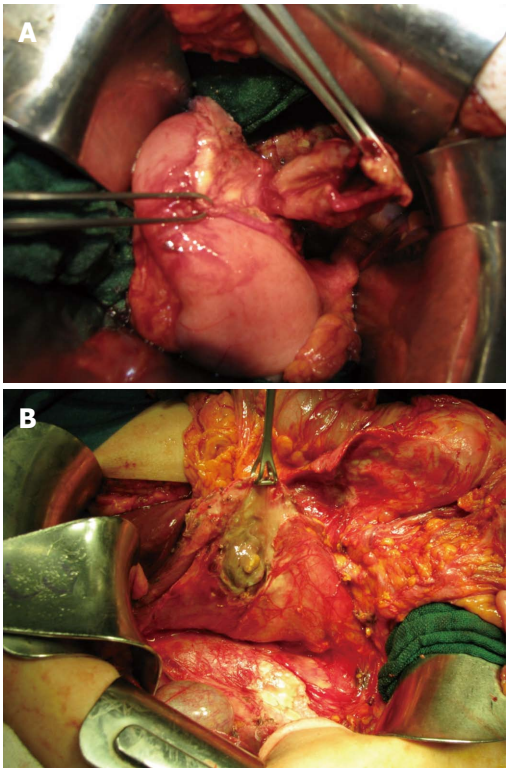

Figure 2 Intraoperative image of case 6 (A) and 7 (B) after a Kocher manoeuvre. A: A perforated duodenal diverticulum was found after performing a Kocher manoeuvre.

Table 1 Results of population characteristics and clinical presentation

Case	Age (yr)	ASA	Symptoms	Shock	Diagnosis	Perforation localization	Follow-up
1	91	3	RUQ acute pain, nausea and vomiting	No	Surgery	D2	Alive at present after 12 yr
2	68	4	Epigastria acute pain, septic shock	Yes	Surgery	D2	Died
3	83	3	RUQ acute pain, nausea and vomiting	No	CT scan	D2	Lost after 5 yr of follow-up
4	78	3	Epigastria acute pain, nausea and vomiting	No	Surgery	D2	Lost after 5 yr of follow-up
5	76	3	Bilateral basithoracic pain	No	CT scan	D2	Lost after 9 yr of follow-up
6	65	3	Epigastria and RUQ acute pain, nausea and vomiting	No	Surgery	D2	Alive after 1 yr of follow-up
7	48	3	RUQ pain irradiating to the back	No	CT scan	D3	Alive after 2 yr of follow-up

ASA: American Society of Anesthesiologists' score; CT: Computed tomography; RUQ: Right upperquadrant.

Table 2 Results of treatment

Case	Localization	Treatment	Morbidity-mortality	Hospital stay (d)
1	D2	Excision, direct duodenal suture and nutritional jejunostomy		26
2	D2	Drain and laparostomy	Died (cardiac comorbidity)	1
3	D2	Excision, direct duodenal suture and nutritional jejunostomy		18
4	D2	Excision and direct duodenal suture	Conservatively treated suture leak on POD day 5	30
5	D2	Gastric tube and antibiotics therapy		16
6	D2	Excision and direct duodenal suture		15
7	D3	Excision, direct duodenal suture, nutritional jejunostomy and bilio-duodenal drain		22

POD: Post-operative day.

The median hospital stay was 21.1 d (range: 15-30 d). No long-term complications were detected (median follow-up of 63 mo).

DISCUSSION

Perforation is an uncommon complication of DD and also one of the most serious[16]. In this paper, we present one of the largest series (seven patients) published to date. The overall outcomes are encouraging, with a low mortality rate and acceptable morbidity. In fact, the most recent review reported rates of morbidity and mortality of 33% and 8%-34% respectively[5]. Our results compare favorably with these data.

Although well known as a possible complication of DD, few reports of perforation can be found in the literature. In fact, Thorson *et al*[5] recently reviewed the available literature and found only 162 cases. The leitmotif remains a difficult preoperative diagnosis. Indeed, the symptoms are often non specific and vague. Yet, one of the most frequent patterns of presentation seems to be right upper abdominal pain associated with nausea and vomiting, as found in our series. Moreover, the differential diagnosis is wide and can be confusing. The most difficult differential diagnosis is a perforated duodenal ulcer, which can show the same pattern in the clinic and on CT scan. Since the wide diffusion of CT, the preoperative diagnosis of perforated DD has increased, and this is currently the best imaging modality available. Although the final diagnosis is often made in the operating room, CT is undeniably helpful and can sometimes differentiate perforated DD from a perforated duodenal ulcer. In addition, perforation may cause retroperitoneal abscesses[16,17]. However, we did not find extended abscesses of the retroperitoneal area in our case series, probably thanks to the early performance of CT scans (maximum delay of 6 h). Therefore, CT is usually the first diagnostic procedure to be performed even though its specificity is below 100%.

In terms of the location of the perforation, the second and third duodenal portions are involved in most cases[5,14], as observed in our series. As a corollary to its rarity, the management of perforated DD remains subject to debate. No surgical guidelines have been published for perforated DD, as only case reports and small series (up to 8 patients) have been reported in the literature[5,16,17]. In general, the surgical approach was considered the treatment of choice. However, several recent cases were treated with bowel rest, a naso-gastric tube and antibiotics, with encouraging results in selected patients[5,15]. If a surgical intervention is highly indicated for unstable patients, the conservative approach deserves consideration since its use appears to be attractive in more stable patients. This option may be particularly useful in a patient of advanced age or in a patient with multiple medical comorbidities who is a prohibitive operative risk[14]. On the other hand, in a patient with mild abdominal symptoms and no evidence of impending sepsis, non-operative management may suffice[14]. Taylor's approach is widely and successfully used for upper digestive perforation and perforated DD could be treated using the same technique. In the present series, the only patient who underwent conservative treatment was selected for such treatment because he presented with mild symptoms and

a clear diagnosis was possible preoperatively. Therefore, in selected patients with a precise CT-scan diagnosis and good clinical condition, conservative treatment can be considered.

In terms of surgical approach, several technical options are available, ranging from local excision to the Whipple procedure, depending on the location of the DD and the inflammatory status[18]. Moreover, laparoscopic diverticulectomy has also been reported to give good results[19]. In their recent review, Thorson *et al*[5] found diverticulectomy to be the most common treatment (49%). In our series, five patients were surgically treated with an almost identical procedure: excision of the DD and direct suture, with a drain placed in the resection area.

Nutritional jejunostomy was performed in three of the five cases and a naso-gastric tube was left in place for at least 7 d. Of note, in one case, a transcystic biliary drain was necessary due to the location of the perforated periampullary DD. This was introduced in order to prevent biliary stenosis in relation to the duodenal suture. Perforation of a DD is a very serious complication and may be fatal. Early CT scan is recommended for diagnosis in suspected cases. Our therapeutic strategy for a perforated DD is resection of the diverticula and direct suture when possible, associated with drainage and placement of a nutritional jejunostomy. A conservative approach is attractive in selected patients.

REFERENCES

1 **Ackermann W**. Diverticula and variations of the duodenum. *Ann Surg* 1943; **117**: 403-413 [PMID: 17858190 DOI: 10.1097/00000658-194303000-00007]
2 **Leivonen MK**, Halttunen JA, Kivilaakso EO. Duodenal diverticulum at endoscopic retrograde cholangiopancreatography, analysis of 123 patients. *Hepatogastroenterology* 1996; **43**: 961-966 [PMID: 8884321]
3 **Suda K**, Mizuguchi K, Matsumoto M. A histopathological study on the etiology of duodenal diverticulum related to the fusion of the pancreatic anlage. *Am J Gastroenterol* 1983; **78**: 335-338 [PMID: 6407301]
4 **Chitambar IA**, SPRINGS C. Duodenal diverticula. *Surgery* 1953; **33**: 768-791 [PMID: 13056877]
5 **Thorson CM**, Paz Ruiz PS, Roeder RA, Sleeman D, Casillas VJ. The perforated duodenal diverticulum. *Arch Surg* 2012; **147**: 81-88 [PMID: 22250120 DOI: 10.1001/archsurg.2011.821]
6 **Umbricht-Sprüngli RE**, Hollinger A, Meier L, Largiadèr F. [Complications of diverticuli of the proximal small intestine. 3 case reports and review of the literature]. *Chirurg* 1992; **63**: 568-571 [PMID: 1505265]
7 **Papalambros E**, Felekouras E, Sigala F, Kiriakopoulos A, Giannopoulos A, Aessopos A, Bastounis E, Mirilas P, Hepp W. Retroperitoneal perforation of a duodenal diverticulum with colonic necrosis -- report of a case. *Zentralbl Chir* 2005; **130**: 270-273 [PMID: 15965883 DOI: 10.1055/s-2005-836529]
8 **JONES TW**, MERENDINO KA. The perplexing duodenal diverticulum. *Surgery* 1960; **48**: 1068-1084 [PMID: 13790597]
9 **Duarte B**, Nagy KK, Cintron J. Perforated duodenal diverticulum. *Br J Surg* 1992; **79**: 877-881 [PMID: 1422745 DOI: 10.1002/bjs.1800790907]
10 **Franzen D**, Gürtler T, Metzger U. [Solitary duodenal diverticulum with enterolith as a rare cause of acute abdomen]. *Swiss Surg* 2002; **8**: 277-279 [PMID: 12520848 DOI: 10.1024/1023-9332.8.6.277]
11 **Poostizadeh A**, Gow KW, Al-Mahmeed T, Allardyce DB. Traumatic perforation of duodenal diverticulum. *J Trauma* 1997; **43**: 370-371 [PMID: 9291392 DOI: 10.1097/00005373-199708000-00031]
12 **Elder J**, Stevenson G. Delayed perforation of a duodenal diverticulum by a biliary endoprosthesis. *Can Assoc Radiol J* 1993; **44**: 45-48 [PMID: 8425156]
13 **Oddo F**, Chevallier P, Souci J, Baque J, Buckley MJ, Fabiani P, Diaine B, Coussement A. [Radiologic aspects of the complications of duodenal diverticula]. *J Radiol* 1999; **80**: 134-140 [PMID: 10209709]
14 **Miller G**, Mueller C, Yim D, Macari M, Liang H, Marcus S, Shamamian P. Perforated duodenal diverticulitis: a report of three cases. *Dig Surg* 2005; **22**: 198-202 [PMID: 16137998 DOI: 10.1159/000087974]
15 **Ames JT**, Federle MP, Pealer KM. Perforated duodenal diverticulum: clinical and imaging findings in eight patients. *Abdom Imaging* 2009; **34**: 135-139 [PMID: 18253777 DOI: 10.1007/s00261-008-9374-x]
16 **Lobo DN**, Balfour TW, Iftikhar SY, Rowlands BJ. Periampullary diverticula and pancreaticobiliary disease. *Br J Surg* 1999; **86**: 588-597 [PMID: 10361174 DOI: 10.1046/j.1365-2168.1999.01121.x]
17 **Andromanakos N**, Filippou D, Skandalakis P, Kouraklis G, Kostakis A. An extended retroperitoneal abscess caused by duodenal diverticulum perforation: report of a case and short review of the literature. *Am Surg* 2007; **73**: 85-88 [PMID: 17249465]
18 **Schnueriger B**, Vorburger SA, Banz VM, Schoepfer AM, Candinas D. Diagnosis and management of the symptomatic duodenal diverticulum: a case series and a short review of the literature. *J Gastrointest Surg* 2008; **12**: 1571-1576 [PMID: 18521693 DOI: 10.1007/s11605-008-0549-0]
19 **Kijima T**, Masuda H, Yoshida S, Tatokoro M, Yokoyama M, Numao N, Saito K, Koga F, Fujii Y, Kihara K. Antimicrobial prophylaxis is not necessary in clean category minimally invasive surgery for renal and adrenal tumors: a prospective study of 373 consecutive patients. *Urology* 2012; **80**: 570-575 [PMID: 22743261 DOI: 10.1089/lap.2010.0346]

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CASE REPORT

Liver blood supply after a modified Appleby procedure in classical and aberrant arterial anatomy

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Abstract

Reported here are two cases of a modified Appleby operation for borderline resectable ductal adenocarcinoma of the pancreatic body, in one of which a R0 distal resection was attended to by excision, not only of the celiac axis, but also of the common and left hepatic arteries in the presence of arterial anatomic variation Michels, type Ⅷb. The possibility and avenues of the maintenance of the blood supply to the left hepatic lobe after surgical aggression of this kind are demonstrated employing computed tomography (CT) and 3-D CT angiography. Furthermore, both cases highlight all important worrisome aspects of pancreatic cancer resectability prediction.

Key words: Cancer; Pancreas; Management; Pancreatectomy; Distal pancreatectomy; Vascular invasion; Computed tomography; Blood supply

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INTRODUCTION

Unlike pancreatic head cancer, pancreatic neck or body cancer is commonly diagnosed at the locally advanced stage after the celiac axis branches, among them the common hepatic artery (CHA), having already been involved by the neoplastic process. In terms of current recommendations, celiac axis (CA) and superior mesenteric artery (SMA) invasion presents a contraindication to pancreatectomy for ductal adenocarcinoma[1,2]. However, in certain instances, excision of the CA together with its branches allows a curative procedure to be performed and obviates arterial reconstruction, incurring a high risk of serious complications. In 1953, while carrying out a distal pancreatectomy along with a gastrectomy for locally advanced gastric carcinoma, Appleby pioneered taking advantage of the chance of the re-establishment of the blood supply to the liver after CA and CHA resection by way of

the constantly existent pancreaticoduodenal arcade from the SMA basin[3]. In 1976, Nimura applied Appleby's technique to treat locally advanced pancreatic body-tail carcinoma[4] and in 1991, Nagino *et al*[5] and Hishinuma *et al*[6] succeeded in preserving the stomach in the absence of its invasion from pancreatic tumor by means of sparing the gastroduodenal and right gastroepiploic arteries (GDA and RGEA), thereby modifying Appleby's operation. By the year 2003, two dozen such operative interventions had been accomplished[5,7-15], at most, but refinements in diagnosis and surgical technique have progressively promoted their growing in number[5,11,15-24]. The modified Appleby procedure case reviews in the literature tend to say nothing about the pattern of the celiac-mesenteric arterial vasculature encountered, in as much as, when dealing with variant arteries and the classical arterial architecture, this sort of surgery can be successfully performed without vascular reconstruction. We give an account of two cases of the modified Appleby operation for pancreatic body borderline resectable cancer, in one of which (as yet not described) a R0 distal resection was accompanied by excision, not only of the CA and the CHA, but left gastric arteries as well in the context of aberrant arteries Michels, type VIIIb.

CASE REPORT

Case 1

On the 12th October, 2011, a 64-year-old woman presented with complaints of constant severe upper abdominal pain relievable with Tramadol administration (four times daily), fatigue and a weight loss of 4 kg in a month. According to the past history, back pain had started 5 mo earlier and had been extending into the lower abdomen. The patient had endured the pain for quite a long time and it was not until October that she sought medical attention and was examined. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed cancer of the pancreatic body and tail with affected CA branches. No evidence of dissemination was observed. Performance status was Eastern Cooperative Oncology Group score of 2, Karnofsky index 70%. On admission, the patient was in a moderately grave condition due to the pain experienced and was asthenic with skin pallor. Pulse was 72/min, regular and good volume. Blood pressure was 110/70 mmHg. Breath sounds were vesicular. The abdomen was soft with tenderness in the epigastrium through the thinned anterior wall of which a solid mass was palpable.

Instrumentally derived findings: Abdominal ultrasound (US) showed evidence of pancreatic body tumor extending to the CA, CHA, splenic artery (SA), superior mesenteric vein (SMV) and confluence of the portal vein (PV). The GDA showed close tumor contact over 1 cm, suspicious for ingrowth. Extrinsic compression of the SMV, PV confluence and CHA was documented.

The CT showed that the liver structure appeared unchanged with no focal lesions. A space occupying mass 25 mm in diameter was visualized in the neck and body of the pancreas. Pancreatic hypertension and atrophy of the pancreas' tail were noted. The duct of Wirsung was shown to be dilated up to 7 mm in the tail portion with a blunt cutoff (interrupted duct sign) at the level of the body of the gland, where tiny 2-3 mm cystic entities were discernable. The SMA was apparently traveling just along the left contour of the growth. The GDA was found to be circumferentially encased by the tumor over a length of 1 cm. An accessory renal artery was visible on the right. The lymph nodes in the pancreatic head and paraaortic regions and along the course of the SMA measured up to 17, 10 and 7-9 mm respectively. The conclusion was adenocarcinoma of the pancreatic neck and body with involvement of the CA, CHA and, probably, GDA and confluence of the PV (Figure 1).

A perivaterian diverticulum, simple left kidney cysts, a splenic cyst, lung emphysema and aortal, coronary and iliac atherosclerosis were identified, classical celiaco-mesenterial arterial anatomy (Michels, type 1) (Figure 2).

Esophagogastroduodenoscopy (EGDS) showed focal gastritis and Paquet's stage 1 upper third esophageal varices.

Endoscopic ultrasound (EUS) showed a tumor of the pancreatic body, presumably adenocarcinoma, with neoplastic process spreading to the CHA, distal third of the CA and confluence of the PV. The new growth was seen to be intimately in contact with the left wall of the GDA over a run of 1 cm. Regional lymph node enlargement, most likely related to their being metastatic, was defined (Figure 3).

Abdominal MRI showed a tumor of the neck-body of the pancreas, atrophy of the parenchyma of the pancreas' tail and pancreatic hypertension in the tail portion of the gland. Infiltration of the retroperitoneal fat with extension encircling the CA, SMA and PV confluence was depicted.

Preoperative concept was of a 64-year-old female diagnosed with a T4NxM0 ductal adenocarcinoma of the pancreatic body with invasion of the CA branches and PV and no evidence for distant metastases. She was deemed to have borderline resectable disease because of suspected tumor encroachment on the GDA. Distal pancreatectomy with resection of the CA and PV was planned. The final extent of the procedure was intended to be decided after intraoperative exploration.

The operation was carried out on the 5th December, 2012. At surgery, no distant metastases were found. A whitish solid tumor taking up the whole of the pancreatic body and growing into the CA trifurcation and CHA with adherence to the left 180° of the uninvolved GDA was discovered. On duplex ultrasound with a clamp across the CHA there was a sufficient arterial blood flow in the liver and the hepatic arterial pulsation was present as before. The lesion was judged resectable. A corpo-caudal pancreatectomy with resection of the CA and its branches was completed (Figure 4). At that, the RGEA was not sacrificed, which provided the gastric blood sup-

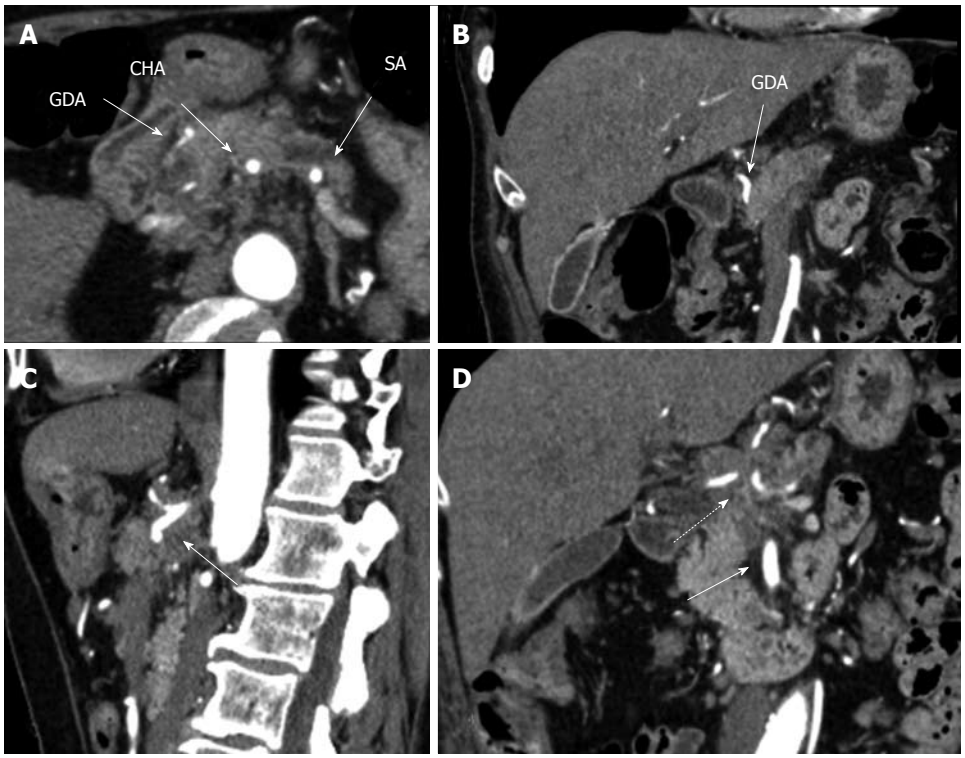

Figure 1 Preoperative computed tomography. Arterial phase. A: Axial image. The common hepatic (CHA) and splenic (SA) arteries present circumferential adjacency to pancreatic body ductal adenocarcinoma. The gastroduodenal artery (GDA) appears to be completely encircled by tumor; B: Frontal view. Computed tomography (CT) evidences circumferential infiltration of GDA; C: The celiac artery (CA) along with CHA springing from it, are completely circumscribed by tumor (arrow); D. All three CA branches (dashed arrow) show circumferential tumor contact. The superior mesenteric artery is unaffected (arrow).

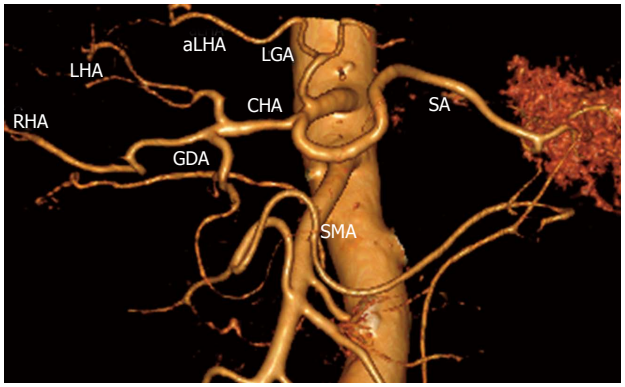

Figure 2 Three-dimensional computed tomography-angiography before surgery. Classical arterial architecture (Michels, type I). Tumor-induced common hepatic (CHA) stenosis is noted. Anatomical variation of type I is observed: CHA trifurcation in the absence of proper hepatic artery. RHA: Right hepatic artery; LHA: Left hepatic artery; GDA: Gastroduodenal artery; LGA: Left gastric artery; SMA: Superior mesenteric artery; SA: Splenic artery; aLHA: Accessory left hepatic artery.

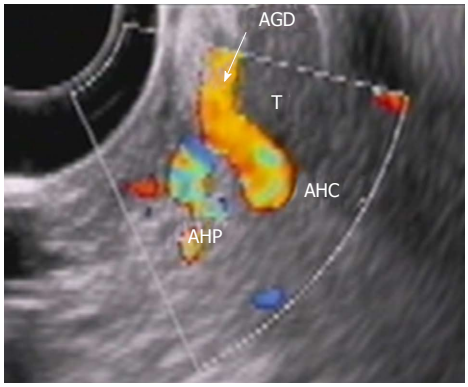

Figure 3 Endoscopic ultrasound. Tumor (T) abutment to gastroduodenal artery (AGD and arrow) without its encasement. HAC: Common hepatic, HAP: Proper hepatic artery.

ply, with the stomach and liver's color remaining unaltered throughout the operative time period.

Post surgery, the patient developed a retroperitoneal pancreatic fluid collection in the projection of the cut edge of the gland with an amylase of 60 000 (pancreatic fistula Class B), which was drained on postoperative day 5. Nine days after the surgery, EGDS recognized areas of gastric mucosa ischemia of mixed (portal and arterial) genesis, ischemic gastropathy. Recurrent hydrothorax was repeatedly addressed with pleural tapping (G3, Dindo-Clavien). After management with antibiotics, antisecretory and anti-ulcer therapy and treatment for diabetes mellitus, the patient's condition stabilized, body temperature returned to normal and complete pain abolition was achieved. The glycemic profile was stable with a blood sugar level of 7-9 mmol/L under insulin therapy and the patient was discharged to receive adjuvant gemcitabine chemotherapy.

Microscopic examination and pathological diagnosis showed a moderately-differentiated pancreatic body-tail adenocarcinoma (pT3N1b, G2) with CA branches and

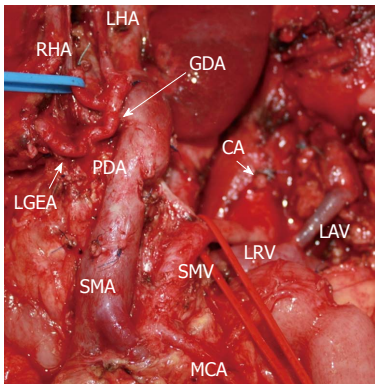

Figure 4 Photograph. View of operating field after distal pancreatectomy with excision of celiac artery (CA) and its branches. Liver and stomach are fed with blood from the superior mesenteric artery (SMA) *via* pancreaticoduodenal arcade (PDA) and, thereafter, through the gastroduodenal artery (GDA). Full-blown right gastro-epiploic artery is found. Superior mesenteric vein (SMV) was resected at the site of confluence with splenic vein. LAV: Left adrenal vein; MCA: Medial colic; RHA: Right hepatic; LHA: Left hepatic arteries; LRV: Left renal vein; LGEA: Left gastro-epiploic artery.

PV involvement. The patient had a R1 distal resection owing to the vascular specimen margin from the sites contacting with the SMV and GDA (Figure 5). The 6 month follow-up CT yielded no evidence for disease recurrence and CT angiography displayed an ample blood flow in the liver and stomach (Figure 6).

Case 2

In May, 2010, a 65-year-old woman consulted a doctor about pain in her right upper abdominal quadrant. On examination, a diagnosis of chronic pancreatitis was made and she was given conservative therapy which was of no benefit. In November 2010, abdominal CT invited by the pain worsening was undertaken and revealed a mass in the pancreatic body.

She entered the Moscow Herzen Institute of Oncology. CT detected an up to 5.6 cm pancreatic body tumor spreading to the CA branches and superior mesenteric arteries. On fine-needle aspiration biopsy, a well-differentiated adenocarcinoma was identified. The neoplasm was considered not to be amenable to resection. 8 courses of a palliative combination chemotherapeutic regimen consisting of 200 mg of eloxatin + 3600 mg of gemzar were instituted.

In July, 2011, the follow-up CT showed no drastic evolution in the disease course with persistent infiltration of the CA, its branches, superior mesenteric and splenic veins and no distant metastases (Figure 7). On CT angiography, variant arterial architecture Michels, type ⅧIb, with a replaced right hepatic artery (rRHA) coming from the SMA and an accessory left hepatic artery (LHA) given off by the left gastric artery (LGA) was determined (Figure 8).

Reasoning from the absence of interval neoplastic progression, we opted for an attempt at a radical procedure. Preoperative diagnosis was a ductal pancreatic body adenocarcinoma, cT4NxM0. Upon abdominal inspection, a pancreatic body solid whitish knobby tumor, up to 3-4 cm in diameter, involving the splenic and CHAs, proximal segment of the CA and LHA with peritumoral fibrosis and contraction in the center was disclosed. On table US demonstrated the blood flow in the left hepatic lobe to be sustained subsequent to briefly clamping the LHA, which encouraged us to undertake a subtotal pancreatectomy with CA excision and resection of the common and left hepatic arteries. As we did so, the GDA was also resected and ligated, that is to say, the pancreaticoduodenal arcade was unlocked (Figure 9). She was discharged on postoperative day 12 after uneventful postoperative recovery to be continued on neoadjuvant gemcitabine chemotherapy.

Conclusion on histological examination was a well-differentiated adenocarcinoma of the pancreatic body, pT2N0M0, G1. Tumor structures, measuring up to 1.2 cm in their greatest dimension, were found throughout an immense fibrotic bulk harboring remnants of pancreatic tissue composed of ductules and atrophic islets (Figure 10). The shortest margin-to-margin distance between the tumor and the specimen was 3 mm and a R0 resection was achieved. No features of post chemotherapeutic changes were identified.

The 12-mo follow-up CT evidenced no disease recurrence, the patient feels well and goes on working as a doctor. There is an adequate arterial blood supply to the liver and stomach on CT angiography. Sufficient arterial nutrition of the left hepatic lobe is afforded by the engagement of the interlobar artery having an extraparenchymal hilar course (Figures 11 and 12).

DISCUSSION

The observations under review might be dually instructive. In the first place, they illustrate the feasibility of the maintenance of the blood flow in the left hepatic lobe after the modified Appleby operation with CHA and LHA resection in the presence of the RHA departing from the SMA. Secondly, both cases pinpoint key bothersome aspects of preoperative determination of pancreatic cancer resectability.

The modified Appleby technique has rightly gained acceptance as an effective approach to the management of pancreatic body cancer in cases of CHA involvement by tumor. We have performed 11 modified Appleby procedures, at 10 of which the classical arterial anatomy, identical to that encountered in Case 1, was found. An aberrant arterial pattern was present only in Case 2. Theoretically, when dealing with most variants in the celiac-mesenteric arterial architecture, this operation is quite safe with regard to the re-establishment of the arterial blood supply to the liver and stomach. Yet, cases with the replaced LHA (Michels, types Ⅳ and ⅧIa) or the CHA (Michels, type X) arising from the LGA[25], as well as the described above situation, when the tumor involvement requires resection of either of the hepatic arteries (more often the LHA), present a real challenge secondary to CA excision. With all the patterns men-

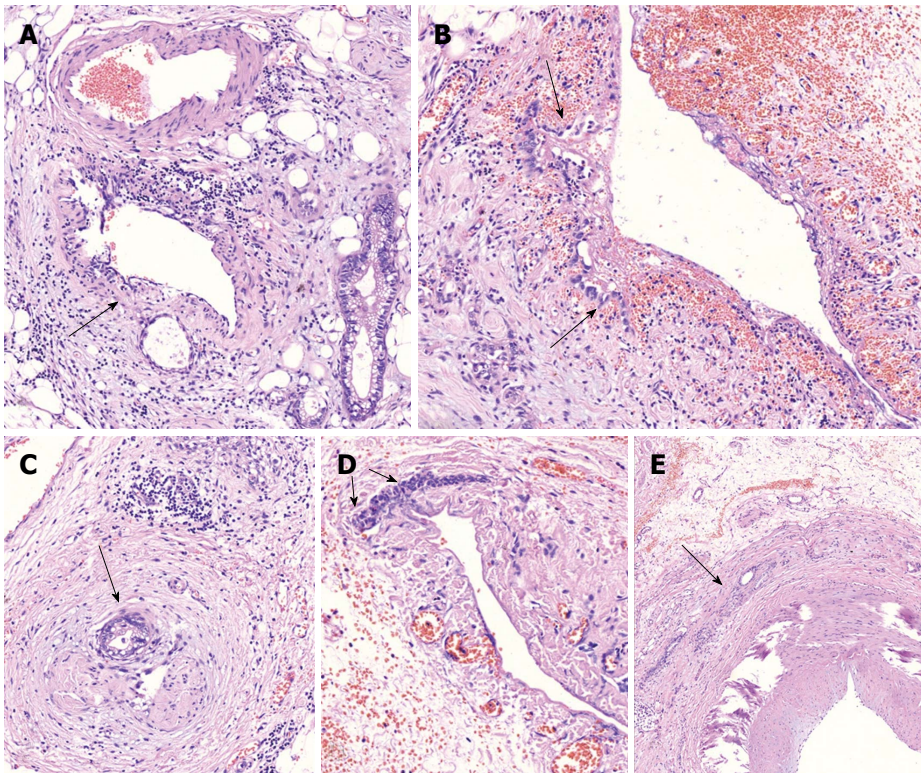

Figure 5 On microscopic examination. A: Perivascular tumor growth (complexes of malignant cells in adventitia of small artery of peripancreatic fat (arrow), HE, × 200; B: Tumor incursion into vein wall (arrow), HE, x 200; C. invasion of the nerve by the tumor (arrow), HE, x 50; D: Vein wall involvement (complexes of malignant cells in media of 2-mm diameter vein (arrows), HE, × 50; E: Tumor complexes in the common hepatic artery adventitia (arrow), HE, × 50.

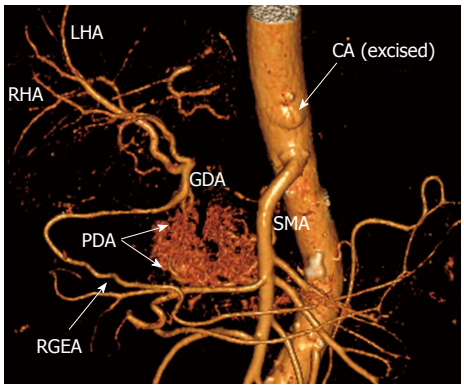

Figure 6 Three-dimensional computed tomography-angiography following distal pancreatectomy with excision of celiac artery and its branches. Blood supply to liver and stomach is delivered from superior mesenteric artery (SMA) *via* pancreaticoduodenal arcade (PDA) and then through gastroduodenal artery (GDA). There is robust right gastro-epiploic artery (RGEA) appearing in its entirety. RHA: Right hepatic artery; LHA: Left hepatic artery; CA: Celiac axis; GDA: Gastroduodenal artery.

tioned above, except variation Michels, type X, in the instance of which Appleby's operation is not feasible without recourse to vascular repair, it is vital to know the sources of the collateral blood supply to the liver to avoid unnecessary arterioplasty.

Investigations of collateral circulation during temporary balloon occlusion of either of the hepatic arteries have first of all been spurred by both the needs of hepatopancreatobiliary surgery and advancements in interventional radiology for hepatopancreatobiliary diseases. The development of collateral blood flow with one of the hepatic arteries being occluded was shown to be a possibility and to depend heavily on the site of vascular obstruction[26,27]. Hepatic interlobar arterial collaterals were exhaustively analyzed in autopsied specimens and corrosion casts[26-30], as well as with radiological studies[31-37] called into being by the evolution of hepatic surgery, transplantation, interventional radiology, endovascular chemotherapy and embolization. Angiography demonstrated the interlobar branch-relayed collateral blood flow between the hepatic arteries[31-37] to be readily noted at the occlusion of either of the hepatic arteries[32,33,37], which was demonstrated by computerized tomographic angiography in our Case 2 (Figure 11). The interlobar arterial collaterals may be responsible for the poor distribution of a chemotherapeutic agent at its selective intraarterial infusion[32]. Injuries to these collateral pathways, participating in the blood supply of the hilar bile ducts, may induce ischemia of the biliary tract after liver resections and biliary surgery[28,29]. The majority of investigators are in agreement that the interlobar collateral is extraparenchymal, passes cranial to the bifurcation of the PVs in the hepatic hilum in close proximity to the bile ducts[32,33,37-40] and makes the crucial contribution of the blood supply to the biliary tract, as well as one of the hepatic lobes in the event of liver major route interruption[29,36,37,41]. So far it has not been clear whether there are transparenchymal branches to connect the hepatic lobes[31,33,36,42].

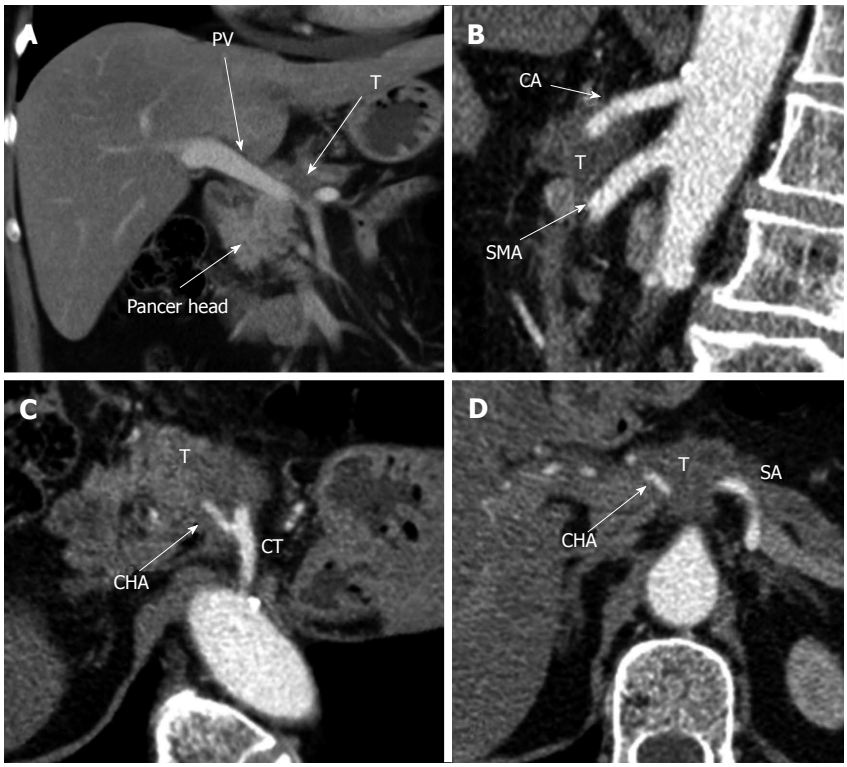

Figure 7 Computed tomography prior to operation. A: Axial view. Venous phase. Hypovascular tumor of pancreatic neck (T) is shown to abut portal vein (PV) trunk. Pancreatic head is demonstrated to be intact; B: Sagittal view. Arterial phase. Circumferential encasement of celiac artery (CA) by hypovascular tumor of pancreatic body and the latter's adherence to anterior aspect of superior mesenteric artery (SMA); C, D: Axial image. Arterial phase. Circumferential contiguity of tumor to CA along with common hepatic (CHA) and splenic (SA), both arising from the former, is visualized. CT: Celiac trunk.

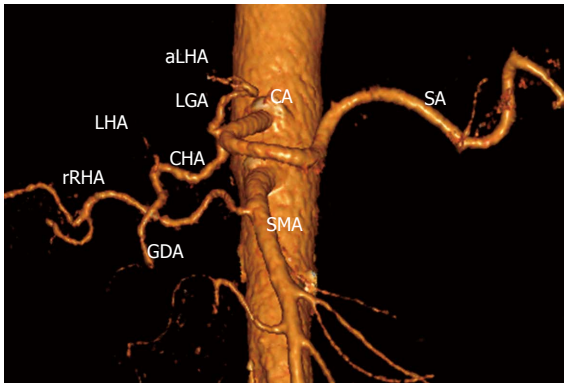

Figure 8 Three-dimensional computed tomography angiography before surgery. Variant arterial anatomy: replaced right hepatic artery (rRHA) originating from superior mesenteric artery (SMA), accessory left hepatic (aLHA) - from left gastric (LGA) (Michels, type Ⅷb). CA: Celiac artery; LHA: Left hepatic artery; SA: Splenic artery; GDA: Gastroduodenal artery; CHA: Common hepatic.

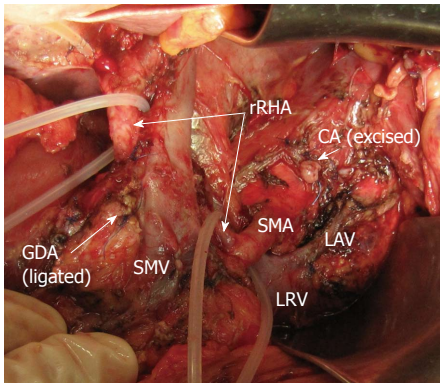

Figure 9 Photograph. View of operating field after distal pancreatectomy with excision of celiac artery (CA), left gastric, common hepatic and left hepatic arteries. Superior mesenteric artery (SMA)-derived blood feeding of right hepatic lobe carried *via* the replaced right hepatic artery (rRHA). Blood supply to stomach is routed from SMA *via* pancreaticoduodenal arcades and then through gastroduodenal artery (GDA) with the latter's proximal segment being resected and ligated. CA: Celiac artery; LAV: Left adrenal vein; LRV: Left renal vein; SMV: Superior mesenteric vein.

Case 2 demonstrates that LHA excision at a distal pancreatectomy with resection of CA and its branches is permissible by virtue of the fact that an arterial blood supply keeps coming to the left hepatic lobe thanks to the availability of the interlobar collateral. In this case, the arterial blood supply to the left hepatic lobe and segment 1 kept being furnished through the interlobar collateral, originating from the rRHA and running in the liver hilum (Figure 12). The evidence for the functioning of the interlobar collateral emerges quite frequently on angiography at chemoembolization of the hepatic arteries or for control of external hemorrhage and/or hemobilia (Figures 13 and 14).

Pancreatic cancer remains one of the most aggressive neoplastic processes and the ways of its management are in the development stage[43,44]. Despite impressive progress attained in the diagnosis and treatment of otherwise sited malignances, the resectability and 5 year

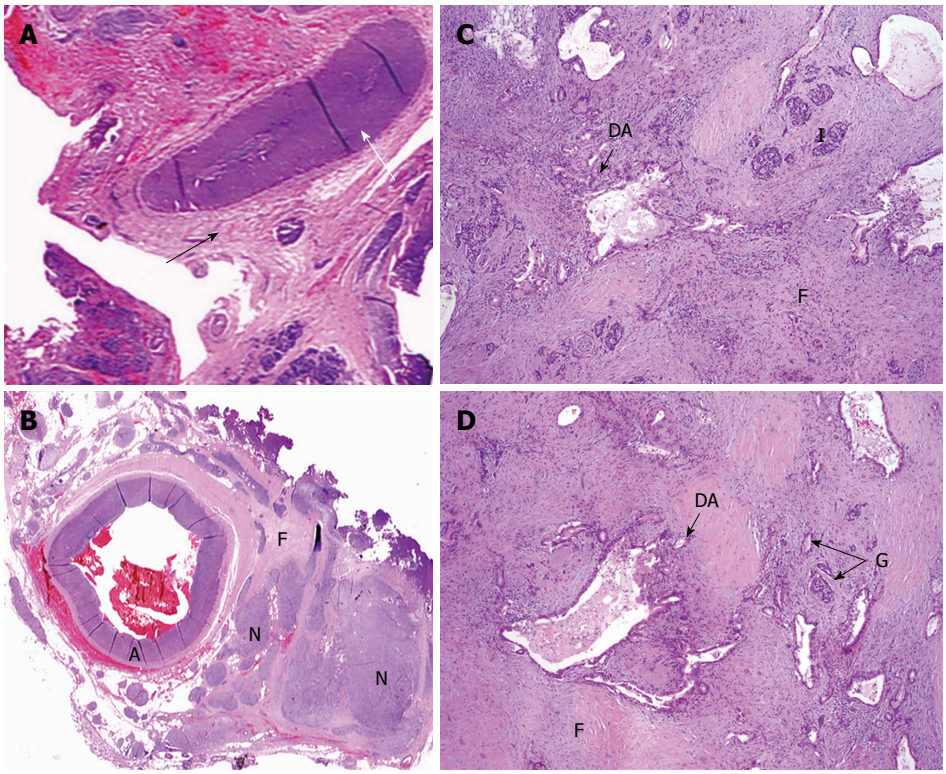

Figure 10 Under microscope. A: Common hepatic (CHA) section obtained from close to the point of its transection (white arrow) amid fibrotic zone (black arrow) along pancreas margin. No evidence of tumor growth (× 5); B: Celiac plexus and trunk area of diffuse fibrosis (F) (× 5); C: Pancreatic tissue with apparent diffuse fibrosis (F), groups of islets left (I) and that of glandular formations of ductal adenocarcinoma of pancreas (DA) (× 50); D: Structures of DA throughout fibrotic tissue (F) containing remnants of pancreatic tissue (atrophic islets and ductules) (HE, × 5). A: Artery; N: Nerve plexus with large ganglion (G).

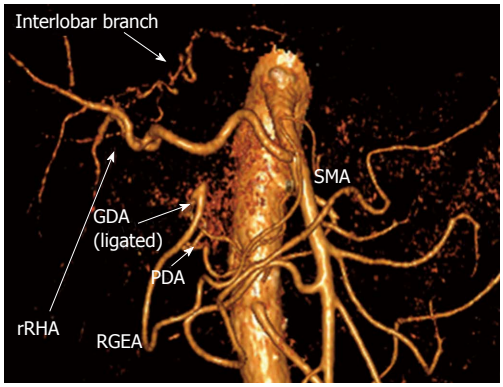

Figure 11 Three-dimensional computed tomography angiography subsequent to distal pancreatectomy with excision of celiac artery, left gastric, common hepatic and left hepatic arteries. Blood supply to right hepatic lobe is provided by superior mesenteric artery (SMA) through the replaced right hepatic artery (rRHA) and that to left hepatic lobe - *via* interlobar collateral anastomosing with rRHA. Stomach is supplied from SMA *via* pancreaticoduodenal artery (PDA) and, thereafter, through gastroduodenal artery (GDA) and right gastro-epiploic artery (RGEA).

survival rates for pancreatic cancer are still very poor with those for pancreatic body and tail of 10% and 10%[45-47] in North America and the Western Europe and of 34% and 18% in Japan respectively[48]. Compared to pancreatic head cancer, typically manifesting itself in jaundice, and for lack of specific symptoms, carcinoma of the pancreatic body is generally recognized at more advanced stages, presenting with rather a sizable tumor, distant metastases and back pain.

The pancreatic body is a fairly modest size across and tumor advancement to the retroperitoneal organs, nerve plexuses, SA, CHA and CA does not take long, which potentially causes the neoplasm to be interpreted as unresectable in compliance with the adopted Jakarta International Community Center classification[1]. Just the same, not only does radical removal of pancreatic body carcinoma with the use of Appleby's technique improve patient life quality, it also significantly prolongs survival, which was attested to, not only in cases of arterial resection necessitating no reconstruction[5,11,13-21], but in those resorting to repair as well[16,23-25].

Completeness (radicality) of resection is one of the dominant independent prognostic factors for pancreatic cancer[46-53]. A curative resection of tumor is the only means of treatment that will hold out a hope of long-term survival for pancreatic cancer patients, although only 10%-15% of them would be eligible for a radical procedure[54]. Preoperative resectability estimation is an outstanding problem of great concern resulting primarily from the intricacies of the involvement evaluation of the major peripancreatic arteries in so far as their actual invasion is regarded as a contraindication to a curative procedure[55-57]. Since CT is invariably rated the gold standard for the diagnosis of pancreatic cancer, it is of critical importance that patients with a resectable tumor

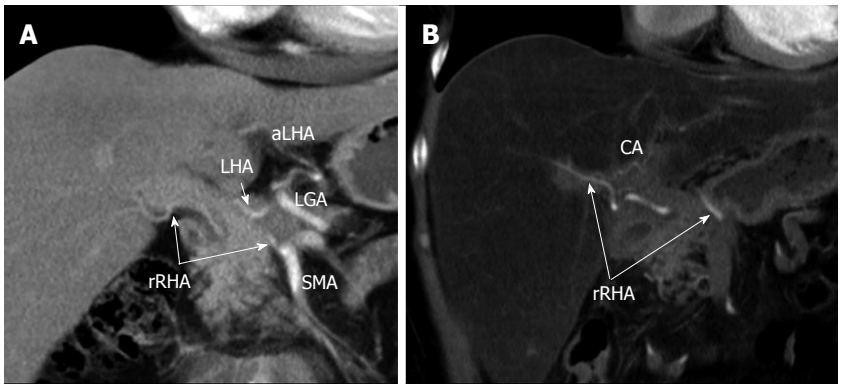

Figure 12 Coronal image. Arterial phase. A: Previous to surgery. Aberrant arterial vasculature (Michels, type Ⅷb): replaced right hepatic artery (rRHA) stemming from superior mesenteric artery (SMA), the left gastric artery (LGA) giving rise to accessorial left hepatic artery (aLHA). No interlobar collateral is detectable; B: Distal pancreatectomy with excision of celiac artery (CA), LGA, common hepatic (CHA) and left hepatic (LHA) arteries. Increased blood flow *via* rRHA is displayed and extra-parenchymal hilar interlobar collateral transmitting blood supply to left hepatic lobe became visible.

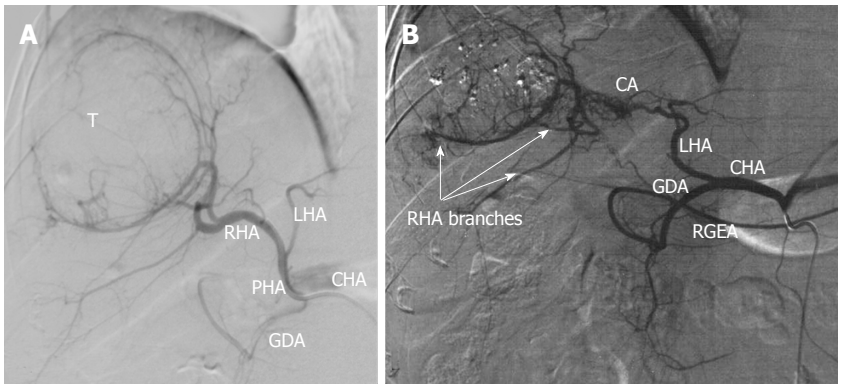

Figure 13 Selective celiacography in a 37-year-old man with firearm (machine gun shots) liver wounds, false aneurysms of left hepatic lobe and hemobilia. A: Classical arterial architecture (Michels, type 1). There is communicating interlobar artery (CA) connecting right and left hepatic arteries (RHA and LHA). Turbulent blood flow is seen in areas of pulsative hematomas (H); B: Control of hemorrhage was achieved with RHA occlusion but arterial branches of right hepatic lobe keep being filled owing to CA-conveyed blood transit from the left hepatic artery (LHA). GDA: Gastroduodenal artery; PHA: Proper hepatic artery; CHA: Common hepatic artery; RGEA: Right gastroepiploic artery; T: Tumor.

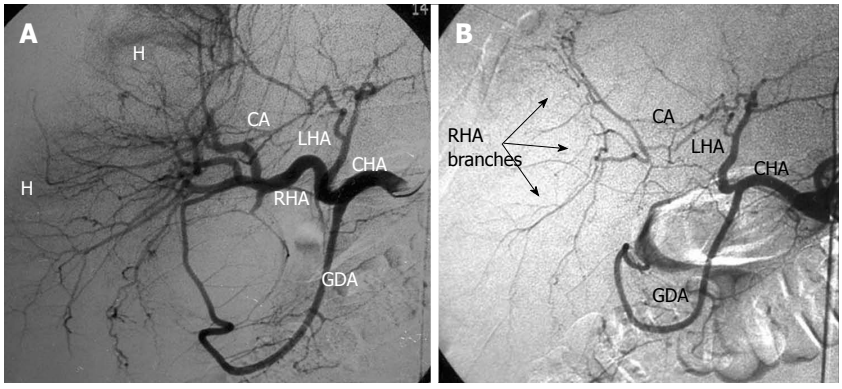

Figure 14 Selective celiacography in a 64-year-old man with hepatocellular cancer. A: Before and after chemoembolization through the right hepatic artery; B: Arterial branches of right hepatic lobe keep being filled owing to communicating interlobar artery (CA)-conveyed blood transit from the left hepatic artery (LHA). GDA: Gastroduodenal artery; CHA: Common hepatic artery; RHA: Right hepatic artery; H: Hematoma.

should not be denied surgery on account of a false-positive CT finding (*i.e.*, when a neoplasm is misinterpreted as nonresectable at CT). On the other hand, what counts for no less is the prevention of an unneeded cumbersome procedure, fraught with devastating morbidity, for an unresectable lesion, keeping in mind that a R2 resection is associated with poor survival.

In the historical series of studies conducted by different authors prior to 2000, from 15% to 70% pancreatic cancer cases thought of as resectable from CT data

turned out to be nonresectable at operation[58-61]. As of now, the sensitivity and specificity of the assessment of vascular involvement, even with a > 90° circular contact and marked vascular deformity (D or E according to Phoa), are reported at 60% and 90% correspondingly[62,63], which indicates that the accuracy of pancreatic cancer resectability appraisal is an elusive troublesome question. Based on the findings reported by various researchers, Li *et al*[64] defined the following CT criteria for major vascular invasion with an exhibited sensitivity of the method of 79% and a specificity of 99%: embedment of the arterial trunk in tumor, encasement by tumor > 180° or > 50% of the vessel circumference coupled with either irregularity of the wall contour or arterial narrowing. Loyer *et al*[65] established that with type A (a fat plane between tumor and vessel) or type B (a normal pancreatic parenchyma separating the tumor from the vessel), the accuracy of the resectability prediction was 95% and Phoa *et al*[62] showed type D (a vascular wall concavity against the tumor to be consistent with a 88% risk for invasion and a 7% predicted resectability) and type E (complete vascular encirclement by tumor) to correlate with a 0% resectability, depending on tumor surface irregularity and vascular deformity. Nevertheless, there is presently no consensus of opinion as to the modality of choice for the assessment of pancreatic cancer extension previous to surgery, since studies that would offer sufficient accuracy are lacking[66,67].

Both our cases demonstrate the unresolved problem of pancreatic cancer resectability determination to be currently pressing, among other reasons, as a consequence of CT being employed for this purpose in the majority of clinics (and quite routinely as a single option). The basic guide to the accuracy of resectability estimation is the ability of a diagnostic technique to identify the presence or absence of invasion of the major peripancreatic arteries. In Case 1, circumferential encasement of the GDA was found on CT and in Case 2, CHA, LHA and CA bifurcation was recognized. At surgery and subsequently under the microscope, the finding in Case 1 proved to be a mere close tumor-artery contact free of ingrowth (which ensured a R1-resection level). In observation 2, the bulk of the tissue misdiagnosed as tumor at CT turned out to be fibrosis with no features of post-therapeutic changes, which in great part enabled a R0 resection level. From strict considerations relying on the belief that the larger is the tumor-vessel contact area, the higher is the likelihood of vascular invasion[68], both cases might have been judged unresectable, as concluded from the CT interpretation[69]. Nonetheless, in both cases, the tumor was found to be resectable, which suggests that it is desirable that CT evidence-based conclusion in favor of unresectability should be confirmed with further clarifying adjunct modalities, such as EUS.

We feel that the salient features of the reported cases might be of equal interest to hepatopancreatobiliary surgeons as well as diagnostic radiologists engaged in this challenging line.

REFERENCES

1 Exocrine and endocrine pancreas. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors.AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010: 241-249

2 Pancreatic Adenocarcinoma Version 2.2012 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines ®). Fort Washington, PA: National Comprehensive Cancer Network, Inc., 2012

3 **Appleby L.** The coeliac axis in the expansion of the operation for gastric carcinoma. *Cancer* 1953; **6:** 704–707 [10.1002/1097-0142(195307)6:4<704::AID-CNCR2820060410>3.0.CO;2-P]

4 **Nimura Y,** Hattori T, Miura K, Nakashima N, Hibi M. Resection of advanced pancreatic body-tail carcinoma by Appleby's operation. *Shujutu* 1976; **30:** 885-889

5 **Nagino M,** Nimura Y, Hayakawa N, Kamiya J, Kondo S. Appleby's operation for pancreas cancer (in Japanese). *Tan to Sui* 1991; **12:** 1361–1368

6 **Hishinuma S,** Ogata Y, Matusui J, Ozawa I, Inada T, Shimizu H, Kotake K, Ikeda T, Koyama Y. Two cases of cancer of the pancreatic body undergoing gastric preservation with distal pancreatectomy combined with resection of the celiac axis. *Nippon Shoukaki Geka Gakkai Zasshi* 1991; 24: 2782-2786

7 **Wada T,** Konishi T. Application of Appleby's operation for double cancer of the stomach and the pancreatic body (in Japanese). *Gekashinryou* 1977; **19:** 1299–301

8 **Hishida Y.** Combined resection of the major vessels — pancreatic resection and retroperitoneal clearance (in Japanese). *Geka* 1979; **41:** 319-323

9 **Imaizumi T,** Nakamura M, Takada T, Fukushima Y, Suzuki S, Yoshikawa T. A case of pancreatic body and tail carcinoma resected by Appleby's operation (in Japanese). *Geka* 1979; **41:** 532–537

10 **Fujita T,** Imaizumi T, Yoshikawa T, Miyagawa S, Hanyu H. A resected pancreatic body and tail carcinoma by Appleby's operation with portal vein resection (in Japanese with English abstract). *Suizo* 1987; **2:** 122–128

11 **Ozaki H**, Kinoshita T, Kosuge T, Yamamoto J, Shimada K, Inoue K, Koyama Y, Mukai K. An aggressive therapeutic approach to carcinoma of the body and tail of the pancreas. *Cancer* 1996; **77**: 2240-2245 [PMID: 8635090 DOI: 10.1002/(SICI)1097-0142(19960601)77]

12 **Mayumi T**, Nimura Y, Kamiya J, Kondo S, Nagino M, Kanai M, Miyachi M, Hamaguchi K, Hayakawa N. Distal pancreatectomy with en bloc resection of the celiac artery for carcinoma of the body and tail of the pancreas. *Int J Pancreatol* 1997; **22**: 15-21 [PMID: 9387020 DOI: 10.1007/BF02803900]

13 **Kimura W**, Han I, Furukawa Y, Sunami E, Futakawa N, Inoue T, Shinkai H, Zhao B, Muto T, Makuuchi M, Komatsu H. Appleby operation for carcinoma of the body and tail of the pancreas. *Hepatogastroenterology* 1997; **44**: 387-393 [PMID: 9164507]

14 **Kondo S**, Katoh H, Omi M, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T, Kanai M, Yano T. Radical distal pancreatectomy with en bloc resection of the celiac artery, plexus, and ganglions for advanced cancer of the pancreatic body: a preliminary report on perfect pain relief. *JOP* 2001; **2**: 93-97 [PMID: 11870330]

15 **Kondo S**, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T. Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally advanced cancer of the pancreatic body. *Langenbecks Arch Surg* 2003; **388**: 101-106 [PMID: 12684805 DOI: 10.1007/s00423-003-0375-5]

16 **Konishi M**, Kinoshita T, Nakagori T, Inoue K, Oda T, Kimata T, Kikuchi H, Ryu M. Distal pancreatectomy with resection of the celiac axis and reconstruction of the hepatic artery for

carcinoma of the body and tail of the pancreas. *J Hepatobiliary Pancreat Surg* 2000; **7**: 183-187 [PMID: 10982611 DOI: 10.1007/s005340050173]
17 **Liu B**. Modified Appleby operation in treatment of distal pancreatic cancer. *Hepatobiliary Pancreat Dis Int* 2003; **2**: 622-625 [PMID: 14627533]
18 **Lin CC**, Chen CL, Cheng YF. Modified extended distal pancreatectomy for carcinoma of body and tail of pancreas. *Hepatogastroenterology* 2005; **52**: 1090-1091 [PMID: 16001636]
19 **Makary MA**, Fishman EK, Cameron JL. Resection of the celiac axis for invasive pancreatic cancer. *J Gastrointest Surg* 2005; **9**: 503-507 [PMID: 15797231 DOI: 10.1016/j.gassur.2004.11.004]
20 **Gagandeep S**, Artinyan A, Jabbour N, Mateo R, Matsuoka L, Sher L, Genyk Y, Selby R. Extended pancreatectomy with resection of the celiac axis: the modified Appleby operation. *Am J Surg* 2006; **192**: 330-335 [PMID: 16920427 DOI: 10.1016/j.amjsurg.2006.05.010]
21 **Hishinuma S**, Ogata Y, Tomikawa M, Ozawa I. Stomach-preserving distal pancreatectomy with combined resection of the celiac artery: radical procedure for locally advanced cancer of the pancreatic body. *J Gastrointest Surg* 2007; **11**: 743-749 [PMID: 17417712 DOI: 10.1007/s11605-007-0143-x]
22 **Fortner JG**. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. *Ann Surg* 1984; **199**: 418-425 [PMID: 6712317 DOI: 10.1097/00000658-198404000-00008]
23 **Tseng JF**, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Gomez HF, Sun CC, Crane CH, Wolff RA, Evans DB. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 2004; **8**: 935-49; discussion 949-50 [PMID: 15585381 DOI: 10.1016/j.gassur.2004.09.046]
24 **Michels NA.** Blood Supply and Anatomy of the Upper Abdominal Organs with a Descriptive Atlas. Philadelphia, PA: Lippincott, 1955
25 **Michels NA**. Newer anatomy of the liver and its variant blood supply and collateral circulation. *Am J Surg* 1966; **112**: 337-347 [PMID: 5917302 DOI: 10.1016/0002-9610(66)90201-7]
26 **Nakao A**, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, Fujii T. Indications and techniques of extended resection for pancreatic cancer. *World J Surg* 2006; **30**: 976-82; discussion 983-4 [PMID: 16736324 DOI: 10.1007/s00268-005-0438-6]
27 **Takeuchi Y**, Arai Y, Inaba Y, Ohno K, Maeda T, Itai Y. Extrahepatic arterial supply to the liver: observation with a unified CT and angiography system during temporary balloon occlusion of the proper hepatic artery. *Radiology* 1998; **209**: 121-128 [PMID: 9769822]
28 **Stapleton GN**, Hickman R, Terblanche J. Blood supply of the right and left hepatic ducts. *Br J Surg* 1998; **85**: 202-207 [PMID: 9501816 DOI: 10.1046/j.1365-2168.1998.00511.x]
29 **Vellar ID**. The blood supply of the biliary ductal system and its relevance to vasculobiliary injuries following cholecystectomy. *Aust N Z J Surg* 1999; **69**: 816-820 [PMID: 10553973 DOI: 10.1046/j.1440-1622.1999.01702.x]
30 **Healey JE**, Schroy PC, Sorensen RJ. The intrahepatic distribution of the hepatic artery in man. *J Int Coll Surg* 1953; **20**: 133-148 [PMID: 13084954]
31 **Charnsangavej C**, Chuang VP, Wallace S, Soo CS, Bowers T. Angiographic classification of hepatic arterial collaterals. *Radiology* 1982; **144**: 485-494 [PMID: 6285413]
32 **Redman HC**, Reuter SR. Arterial collaterals in the liver hilus. *Radiology* 1970; **94**: 575-579 [PMID: 5413898]
33 **Koehler RE**, Korobkin M, Lewis F. Arteriographic demonstration of collateral arterial supply to the liver after hepatic artery ligation. *Radiology* 1975; **117**: 49-54 [PMID: 1162072]
34 **Chuang VP**, Wallace S. Hepatic arterial redistribution for intraarterial infusion of hepatic neoplasms. *Radiology* 1980; **135**: 295-299 [PMID: 7367615]
35 **Ibukuro K**, Tsukiyama T, Mori K, Inoue Y. The congenital anastomoses between hepatic arteries: angiographic appearance. *Surg Radiol Anat* 2000; **22**: 41-45 [PMID: 10863746 DOI: 10.1007/s00276-000-0041-3]
36 **Miyazaki M**, Ito H, Nakagawa K, Ambiru S, Shimizu H, Yoshidome H, Shimizu Y, Okaya T, Mitsuhashi N, Wakabayashi Y, Nakajima N. Unilateral hepatic artery reconstruction is unnecessary in biliary tract carcinomas involving lobar hepatic artery: implications of interlobar hepatic artery and its preservation. *Hepatogastroenterology* 2000; **47**: 1526-1530 [PMID: 11148993]
37 **Tohma T**, Cho A, Okazumi S, Makino H, Shuto K, Mochiduki R, Matsubara K, Gunji H, Ochiai T. Communicating arcade between the right and left hepatic arteries: evaluation with CT and angiography during temporary balloon occlusion of the right or left hepatic artery. *Radiology* 2005; **237**: 361-365 [PMID: 16118153 DOI: 10.1148/radiol.2371040919]
38 **Chen WJ,** Ying DJ, Liu ZJ, He ZP. Analysis of the arterial supply of the extrahepatic bile ducts and its clinical significance. *Clin Anat* 1999; **12:** 245–249 [DOI: 10.1002/(SICI)1098-2353(1999)12: 4 <245::AID-CA2>3.0]
39 **Cho A**, Okazumi S, Takayama W, Takeda A, Iwasaki K, Sasagawa S, Natsume T, Kono T, Kondo S, Ochiai T, Ryu M. Anatomy of the right anterosuperior area (segment 8) of the liver: evaluation with helical CT during arterial portography. *Radiology* 2000; **214**: 491-495 [PMID: 10671598]
40 **Cho A**, Okazumi S, Yoshinaga Y, Ishikawa Y, Ryu M, Ochiai T. Relationship between left biliary duct system and left portal vein: evaluation with three-dimensional portocholangiography. *Radiology* 2003; **228**: 246-250 [PMID: 12738876 DOI: 10.1148/radiol.2281020740]
41 **Segall H.** An experimental anatomical investigation of blood and bile channels of the liver. *Surg Gynecol Obstet* 1923; **37:** 152–178
42 **Fan ST**, Lo CM, Liu CL, Tso WK, Wong J. Biliary reconstruction and complications of right lobe live donor liver transplantation. *Ann Surg* 2002; **236**: 676-683 [PMID: 12409675 DOI: 10.1097/00000658-200211000-00019]
43 **Tsiotos GG**, Farnell MB, Sarr MG. Are the results of pancreatectomy for pancreatic cancer improving? *World J Surg* 1999; **23**: 913-919 [PMID: 10449820 DOI: 10.1007/s002689900599]
44 **Yamaguchi K**, Shimizu S, Yokohata K, Noshiro H, Chijiiwa K, Tanaka M. Pancreatic carcinoma: reappraisal of surgical experiences in one Japanese university hospital. *Hepatogastroenterology* 1999; **46**: 3257-3262 [PMID: 10626197]
45 **Lillemoe KD**, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: indications and outcomes in 235 patients. *Ann Surg* 1999; **229**: 693-698; discussion 698-700 [PMID: 10235528 DOI: 10.1097/00000658-199905000-00012]
46 **Allema JH**, Reinders ME, van Gulik TM, Koelemay MJ, Van Leeuwen DJ, de Wit LT, Gouma DJ, Obertop H. Prognostic factors for survival after pancreaticoduodenectomy for patients with carcinoma of the pancreatic head region. *Cancer* 1995; **75**: 2069-2076 [PMID: 7697596 DOI: 10.1002/1097-0142(19950415)75:]
47 **Sohn TA,** Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas — 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; **4:** 567-579 [DOI: 10.1016/S1091-255X(00)80105-5]
48 **Doi R**, Imamura M, Hosotani R, Imaizumi T, Hatori T, Takasaki K, Funakoshi A, Wakasugi H, Asano T, Hishinuma S, Ogata Y, Sunamura M, Yamaguchi K, Tanaka M, Takao S, Aikou T, Hirata K, Maguchi H, Aiura K, Aoki T, Kakita A, Sasaki M, Ozaki M, Matsusue S, Higashide S, Noda H, Ikeda S, Maetani S, Yoshida S. Surgery versus radiochemotherapy for resectable locally invasive pancreatic cancer: final results of a randomized multi-institutional trial. *Surg Today* 2008; **38**: 1021-1028 [PMID: 18958561]
49 **Nagakawa T**, Sanada H, Inagaki M, Sugama J, Ueno K,

Konishi I, Ohta T, Kayahara M, Kitagawa H. Long-term survivors after resection of carcinoma of the head of the pancreas: significance of histologically curative resection. *J Hepatobiliary Pancreat Surg* 2004; **11**: 402-408 [PMID: 15619016 DOI: 10.1007/s00534-004-0917-4]

50 **Trede M**, Richter A, Wendl K. Personal observations, opinions, and approaches to cancer of the pancreas and the periampullary area. *Surg Clin North Am* 2001; **81**: 595-610 [PMID: 11459274 DOI: 10.1016/S0039-6109(05)70146-8]

51 **Richter A**, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. *World J Surg* 2003; **27**: 324-329 [PMID: 12607060 DOI: 10.1007/s00268-002-6659-z]

52 **Benassai G,** Mastrorilli M, Quarto G, Cappiello A, Giani U, Forestieri P, Mazzeo F. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. *J Surg Oncol* 2000; **73:** 212-218 [DOI: 10.1002/(SICI)1096-9098(200004)73: 4 <212::AID-JSO5>3.0]

53 **Wagner M**, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004; **91**: 586-594 [PMID: 15122610 DOI: 10.1002/bjs.4484]

54 **Beger HG**, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. *World J Surg* 2003; **27**: 1075-1084 [PMID: 12925907 DOI: 10.1007/s00268-003-7165-7]

55 **Hosten N**, Lemke AJ, Wiedenmann B, Böhmig M, Rosewicz S. Combined imaging techniques for pancreatic cancer. *Lancet* 2000; **356**: 909-910 [PMID: 11036898 DOI: 10.1016/S0140-6736(00)02683-0]

56 **Vargas R**, Nino-Murcia M, Trueblood W, Jeffrey RB. MDCT in Pancreatic adenocarcinoma: prediction of vascular invasion and resectability using a multiphasic technique with curved planar reformations. *AJR Am J Roentgenol* 2004; **182**: 419-425 [PMID: 14736675]

57 **Romijn MG**, Stoker J, van Eijck CH, van Muiswinkel JM, Torres CG, Laméris JS. MRI with mangafodipir trisodium in the detection and staging of pancreatic cancer. *J Magn Reson Imaging* 2000; **12**: 261-268 [PMID: 10931589]

58 **Fuhrman GM,** Charnsangavej C, Abbruzzese JL, Cleary KR, Martin RG, Fenoglio CJ, Evans DB. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am J Surg* 1994; **167:** 104–113 [DOI: 10.1016/0002-9610(94)90060-4]

59 **Megibow AJ**, Zhou XH, Rotterdam H, Francis IR, Zerhouni EA, Balfe DM, Weinreb JC, Aisen A, Kuhlman J, Heiken JP. Pancreatic adenocarcinoma: CT versus MR imaging in the evaluation of resectability--report of the Radiology Diagnostic Oncology Group. *Radiology* 1995; **195**: 327-332 [PMID: 7724748]

60 **Bluemke DA**, Cameron JL, Hruban RH, Pitt HA, Siegelman SS, Soyer P, Fishman EK. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology* 1995; **197**: 381-385 [PMID: 7480681]

61 **Diehl SJ**, Lehmann KJ, Sadick M, Lachmann R, Georgi M. Pancreatic cancer: value of dual-phase helical CT in assessing resectability. *Radiology* 1998; **206**: 373-378 [PMID: 9457188]

62 **Phoa SS**, Tilleman EH, van Delden OM, Bossuyt PM, Gouma DJ, Laméris JS. Value of CT criteria in predicting survival in patients with potentially resectable pancreatic head carcinoma. *J Surg Oncol* 2005; **91**: 33-40 [PMID: 15999356 DOI: 10.1002/jso.20270]

63 **Lopez Hänninen E**, Amthauer H, Hosten N, Ricke J, Böhmig M, Langrehr J, Hintze R, Neuhaus P, Wiedenmann B, Rosewicz S, Felix R. Prospective evaluation of pancreatic tumors: accuracy of MR imaging with MR cholangiopancreatography and MR angiography. *Radiology* 2002; **224**: 34-41 [PMID: 12091659 DOI: 10.1148/radiol.2241010798]

64 **Li H**, Zeng MS, Zhou KR, Jin DY, Lou WH. Pancreatic adenocarcinoma: the different CT criteria for peripancreatic major arterial and venous invasion. *J Comput Assist Tomogr* 2005; **29**: 170-175 [PMID: 15772532 DOI: 10.1097/01.rct.0000155060.73107.83]

65 **Loyer EM**, David CL, Dubrow RA, Evans DB, Charnsangavej C. Vascular involvement in pancreatic adenocarcinoma: reassessment by thin-section CT. *Abdom Imaging* 1996; **21**: 202-206 [PMID: 8661548 DOI: 10.1007/s002619900046]

66 **Schima W**, Függer R, Schober E, Oettl C, Wamser P, Grabenwöger F, Ryan JM, Novacek G. Diagnosis and staging of pancreatic cancer: comparison of mangafodipir trisodium-enhanced MR imaging and contrast-enhanced helical hydro-CT. *AJR Am J Roentgenol* 2002; **179**: 717-724 [PMID: 12185052]

67 **Sperti C**, Pasquali C, Decet G, Chierichetti F, Liessi G, Pedrazzoli S. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. *J Gastrointest Surg* 2005; **9**: 22-8; discussion 28-9 [PMID: 15623441 DOI: 10.1016/j.gassur.2004.10.002]

68 **Springett GM**, Hoffe SE. Borderline resectable pancreatic cancer: on the edge of survival. *Cancer Control* 2008; **15**: 295-307 [PMID: 18813197]

69 **Varadhachary GR**, Tamm EP, Crane C, Evans DB, Wolff RA. Borderline resectable pancreatic cancer. *Curr Treat Options Gastroenterol* 2005; **8**: 377-384 [PMID: 16162303]

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CASE REPORT

Mesenteric paraganglioma: Report of a case

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Abstract

We report a rare case of paraganglioma that developed in the mesentery of terminal ileum. A 78-year-old woman complained of right-sided abdominal pain. Abdominal computed tomography revealed a solid heterogeneously enhanced mass in the right lower abdomen. The tumor was laparoscopically excised. The mesenteric tumor was well circumscribed, ovoid, and encapsulated and measured 3 cm × 1.5 cm × 1.5 cm. Histological examination showed a cellular neoplasm comprised of nests and groups of tumor cells separated by fibrovascular connective tissue, giving a characteristic nested Zellballen pattern. Immunohistochemically, the tumor cells were positive for chromogranin, synaptophysin, CD56, and vimentin and negative for cytokeratins, SMA, CD34, CD117/c-kit and S100. On the basis of histologic and immunohistochemical features, a diagnosis of mesenteric paraganglioma was made. The operative and postoperative courses were unremarkable, and the patient was discharged on postoperative day 7. She was doing well 1 year after the surgery with no signs of recurrence. Extra-adrenal paragangliomas most commonly develop adjacent to the aorta, particularly the area corresponding to the organ of Zuckerkandl. Mesenteric paraganglioma, as in our case, is extremely rare; only 11 cases have been reported in the literature. We herein discuss the clinical findings of these cases.

Key words: Mesenteric tumor; Extra-adrenal paraganglioma; Pheochromocytoma; Surgical management; Preoperative diagnosis

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INTRODUCTION

Paraganglia are groups of morphologically and cytochemically similar cells derived from the neural crest. They include such tissues as the adrenal medulla, carotid and aortic bodies, organs of Zuckerkandl, and other unnamed paraganglia in the distribution of sympathetic and parasympathetic nerves.

Paragangliomas are uncommon tumors arising from the neuroendocrine elements (chief cells) of the paraganglia. However, they have been described in virtually every site in which normal paraganglia are known to occur; only 5%-10% of sporadic paragangliomas are extra-adrenal[1-3]. Paraganglioma as a mesenteric mass is extremely rare, and only occasional reports have been published. The present case report describes a quite rare mesenteric paraganglioma, including its imaging features and histopathological characteristics. In addition, a review of the current literature summarizes the clinical findings associated with mesenteric paragangliomas.

CASE REPORT

A 78-year-old woman, who underwent distal gastrectomy for early gastric cancer in 1994 and total thyroidectomy for papillary thyroid carcinoma in 2000 was followed up at our hospital. In June 2010, she complained of right-sided abdominal pain. Abdominal computed tomography (CT) revealed a solid mass, 16 mm × 22 mm × 25 mm in size, in the right lower abdomen. Contrast-enhanced CT showed a smoothly marginated, heterogeneously enhanced hypervascular tumor adjacent to the right major psoas muscle (Figure 1A and B). Magnetic resonance imaging (MRI) showed that the lesion was hypointense on T1-weighted images and hyperintense on T2-weighted images. After the bolus infusion of gadolinium chelate, the lesion had marked contrast enhancement on T1-weighted images (Figure 1C-E). Whole-body ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) was negative (Figure 1F), and subsequent upper gastrointestinal endoscopy and colonoscopy were not remarkable. Laboratory studies yielded normal blood chemistry and hematology results. The carcinoembryonic antigen and carbohydrate antigen 19-9 levels were both within normal limits. In retrospect, follow-up CT after gastrectomy in 2002 already showed the tumor, which was 16 mm × 13 mm × 15 mm in size and was not pointed out at that time. For 8 years, the tumor had been slowly but definitely growing.

For a definitive diagnosis, surgical resection was recommended to the patient, and she was admitted to our hospital. Physical examination showed a blood pressure of 118/80 mmHg and a regular pulse of 68 bpm. On angiography, the tumor appeared as a hypervascular lesion fed by the superior mesenteric artery (Figure 1G and H). Before surgery, although the differential diagnosis included gastrointestinal stromal tumors, leiomyoma and Castleman's disease, we could not definitively diagnose this tumor.

In March 2011, exploratory laparoscopy confirmed a solid, brownish-red mass in the mesentery of the terminal ileum. There was no lymph node swelling or ascites. Throughout the exploration, there was no remarkable fall or rise in blood pressure. The mass was excised under laparoscopy without ileum resection. Grossly, the mesenteric mass was well circumscribed, ovoid, and encapsulated and measured 3 cm × 1.5 cm × 1.5 cm (Figure 2A). Histological examination showed a cellular neoplasm comprised of nests and groups of tumor cells separated by fibrovascular connective tissue, giving a characteristic nested Zellballen pattern (Figure 2B). Immunohistochemically, the tumor cells were positive for chromogranin, synaptophysin, CD56, and vimentin and negative for cytokeratins, SMA, CD34, CD117/c-kit, and S100. The proportion of Ki-67-positive cells was low (Figure 2C-E).

On the basis of histologic and immunohistochemical features, a diagnosis of mesenteric paraganglioma was made. The operative and postoperative courses were unremarkable, and the patient was discharged on postoperative day 7. She was doing well 1year after the surgery with no signs of recurrence.

DISCUSSION

Paraganglioma is a rare tumor of neural crest cell origin that arises from sympathetic or parasympathetic neural paraganglia. While the most common location of paragangliomas is the adrenal medulla, where they give rise to pheochromocytomas, approximately 5%-10% of sporadic paragangliomas occur in extra-adrenal sites[1-4]. Although extra-adrenal paragangliomas may develop in every site in which normal paraganglia exist, 70%-85% of cases actually occur intra-abdominally, most commonly adjacent to the aorta and particularly the area corresponding to the organ of Zuckerkandl[3,4]. Paragangliomas that develop in the mesentery, as in our case, are extremely rare, with only 11 cases in the literature[3] (Table 1).

As shown in Table 1, there appears to be a marked predilection for females (9:3), which contrasts with the slight male predominance (1.3:1) reported for retroperitoneal paraganglioma[5,6]. At the time of diagnosis, most patients are older (median, 57.5 years of age) than those with retroperitoneal paraganglioma (median, 39-43 years of age[4-6]). No significant difference was noted in the size of mesenteric (average, 9.3 cm) and retroperitoneal tumors (average, 7.4-10.5 cm[4-6]).

The pathogenesis of paragangliomas is not fully understood. They may be either sporadic or hereditary. Overall, as many as 10%-50% of paragangliomas are considered to be hereditary[7]. Hereditary paragangliomas are multicentric in 20%-50% of cases[8,9], whereas sporadic paragangliomas are multicentric in 10% of cases. In hereditary cases, they may be associated with multiple endocrine neoplasia type 2, von Hippel-Lindau disease, familial paraganglioma, Carney triad and neurofibromatosis type 1[10]. For this reason, especially in patients diagnosed before 50 years of age and in those who present with bilateral, multifocal, and malignant paragangliomas, genetic testing may be beneficial[11]. In the present case, the tumor was solitary and the patient was a 78-year-old woman with no history of genetic disorders; thus, genetic screening was not performed.

From a diagnostic viewpoint, functional tumors are easier to diagnose. Most patients undergo paroxysmal episodic hypertension and the typical triad of symptoms associated with pheochromocytoma: palpitations, headache, and profuse sweating. When functional paraganglioma is suspected, biochemical analysis of catecholamine hypersecretion should precede any form of imaging.

However, a majority of extra-adrenal paraganglioma is nonfunctional[11], as in our case. A large proportion of these tumors are incidentally discovered in normotensive patients during imaging evaluation for other reasons. In addition, the CT features of extra-adrenal paraganglioma include a nonspecific soft tissue density and overlap those of other neoplasms. Specifically, tumors of neural or mesodermal origin and those of metastatic

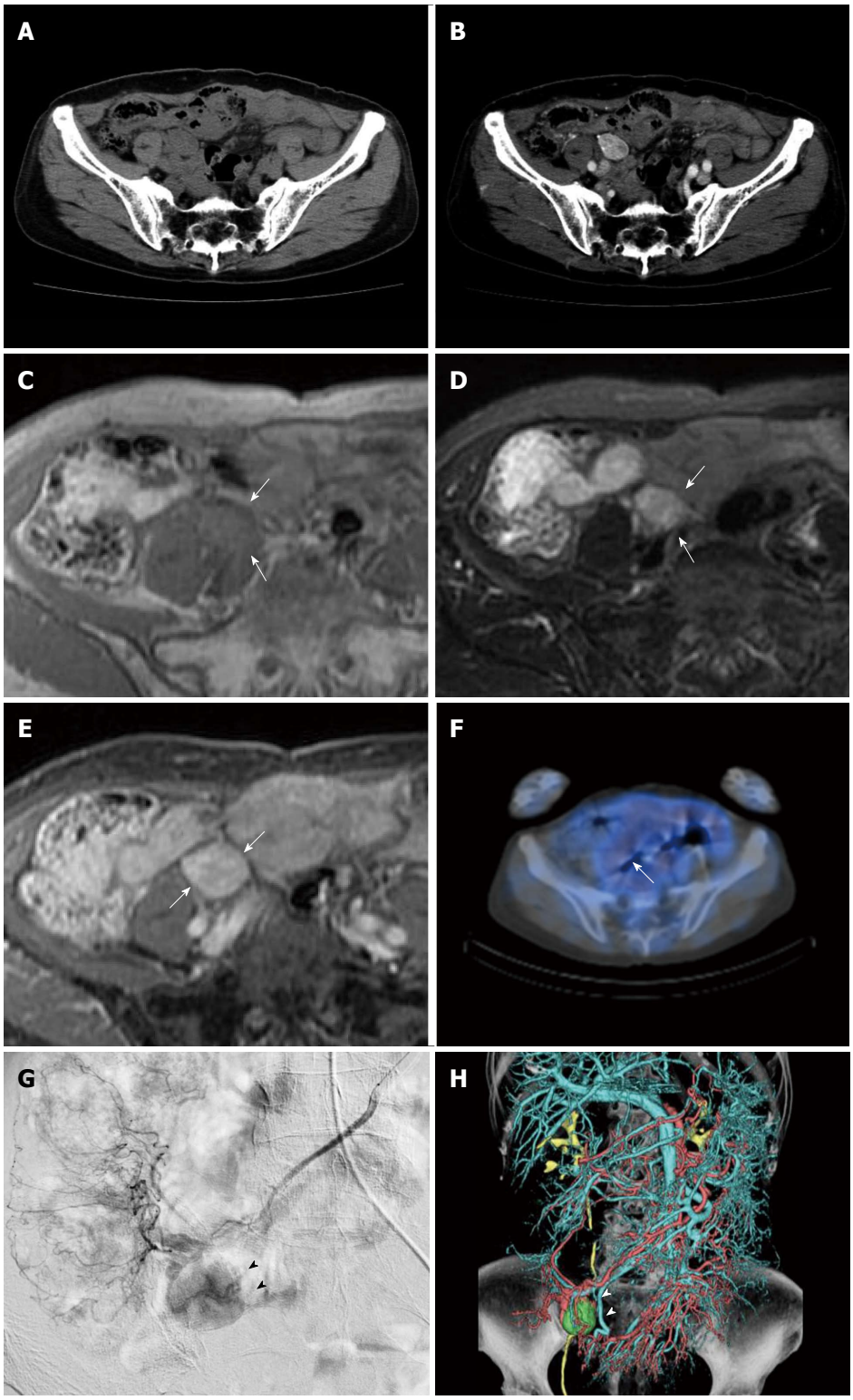

Figure 1 Imaging features of tumor (white arrows) before treatment. A: Axial plain; B: contrast-enhanced computed tomography (CT), CT shows a smoothly marginated, heterogeneously enhanced tumor adjacent to the right major psoas muscle, 16 mm × 22 mm × 25 mm in size; C: T1-weighted magnetic resonance image shows a well defined, isointense mass; D: On T2-weighted images, the mass shows heterogeneous high intensity; E: On T1-weighted images after a bolus infusion of gadolinium chelate, the mass had marked contrast enhancement; F: Positron emission tomography-CT scan was negative; G: Superior mesenteric arteriography displays a markedly hypervascular mass (black arrow heads) adjacent to the terminal ileum; H: Volume rendering image acquired from angio-CT (white arrow heads).

disease must be considered[1]. Thus, because of their clinical manifestation and the overlap with other tumors in terms of medical imaging findings, the preoperative diagnosis of extra-adrenal paraganglioma is usually difficult. Especially when extra-adrenal paragangliomas arise from unusual sites, as in the present case, accurate diagnosis is seldom made preoperatively (Table 1).

The MRI characteristics of our case are quite typi-

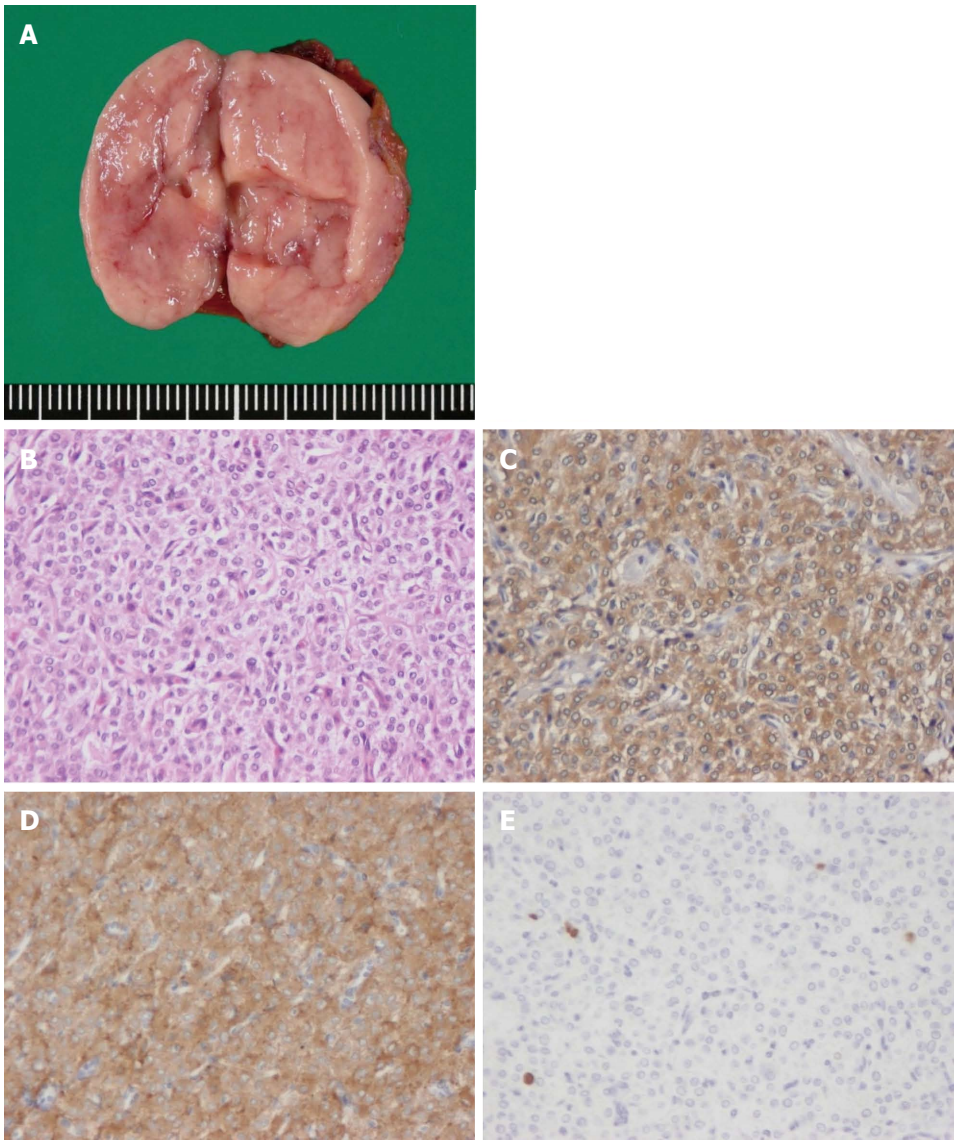

Figure 2 Macroscopic findings and pathological features of the resected tumor. A: Gross findings of the resected specimen. The tumor was encapsulated and measured 3 cm × 1.5 cm × 1.5 cm; B: The paraganglioma comprised a dual cell population arranged in a characteristic nested Zellballen pattern (HE stain, × 400); C: Immunohistochemistory of Chromogranin A, × 400; D: Synaptophysin were strongly positive and confirmed a neuroendocrine origin, supporting the diagnosis of paraganglioma, × 400; E: The MIB-1 labeling index, × 400.

cal for paraganglioma. Paragangliomas have low signal intensity on T1-weighted images and enhance strongly after administration of contrast material. On T2-weighted images, they appear hyper intense. In addition, a speckled appearance with multiple flow voids is typical in tumors > 2 cm in diameter[12]. Angiography was thus useful to outline the location and vascular supply of the tumor in our case; theoretically, however, clinically silent functional tumors should be ruled out by urine analysis before manipulation.

In functional paraganglioma, ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy is the best imaging study for a preoperative diagnosis. MIBG scintigraphy may also be helpful to rule out clinically silent cases, but the specificity for diagnosis of nonfunctional paraganglioma is unclear[13]. In certain cases, FDG-PET may be indicated to investigate metastatic disease[7]. It was recently reported that the newest technique using fluorine-18-dihydroxyphenylalanine-PET imaging offers even higher accuracy than MIBG scintigraphy in the localization of paragangliomas[14].

In the case described here, diagnostic imaging played a very important role preoperatively to determine tumor localization, vascularity, and extent of disease. Differential diagnosis including gastrointestinal stromal tumors, leiomyoma, malignant lymphoma, Castleman's disease and other metastatic tumor could be made preoperatively. However, pitfall for misdiagnosis in our case was tumor location. Because of the tumor location away from the para-aortic area, a preoperative diagnosis of paraganglioma could not be made. Although rare, paraganglioma should be included in the preoperative differential diagnosis of solid hypervascular mesenteric tumors.

The treatment of choice for paraganglioma is surgi-

Table 1 Clinical characteristics of the 12 reported cases of mesenteric paraganglioma

No. of cases	Ref.	Age (yr)	Sex	Location	Symptoms	Size (cm)	Hyperten-sion	Preoperative diagnosis	Surgical procedures	Prognosis
1	Arean *et al*[18]	32	M	Mesentery of the small intestine	Nausea, vomiting, diarrhea	10 × 7 × 6	-	Abdominal mass	Resection of the intestine and its mesentery along with mass	8 mo: Alive without recurrence
2	Carmichael *et al*[20]	62	F	Mesentery of the small intestine	Nausea, vomiting, back pain	3.2	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	Not documented
3	Tanaka *et al*[20]	29	F	Descending colon	Nausea, vomiting	10 × 9 × 7	-	Retroperitoneal mass	Resection of themass	32 mo: Alive without recurrence
4	Ishikura *et al*[21]	33	F	Sigmoid colon	Lower abdominal pain, dysuria	15 × 15 × 15	-	Ovarian tumor	Resection of the sigmoid colon and its mesentery along with mass	Not documented
5	Onoue *et al*[22]	38	F	Mesentery of the small intestine	None	4.5 × 3.2	-	Mesenteric tumor	Resection of the intestine and its mesentery along with mass	24 mo: Alive without recurrence
6	Jaffer *et al*[3]	76	M	Mesentery of the small intestine	Abdominal mass, vomiting, diarrhea	8.5 × 8	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	Not documented
7	Muzaffar *et al*[23]	76	F	Mesentery of the small intestine	Abdominal mass	20 × 15	-	Abdominal mass	Not documented	15 mo: Alive without recurrence
8	Ponsky *et al*[24]	35	F	Mesentery of the small intestine	Abdominal mass, headache	5.5	+	Abdominal mass	Resection of the intestine and its mesentery along with mass	24 mo: Alive without recurrence
9	Kudoh *et al*[25]	72	F	Mesentery of the small intestine (ileum)	Abdominal pain and mass	10 × 9 × 9	-	Mesenteric tumor	Resection of segment of ileum and mesentery containing mass	12 mo: Alive without recurrence
10	Nobeyama *et al*[26]	53	M	Mesentery of the small intestine (ileum)	Abdominal mass	15 × 10 × 7	-	Abdominal mass	Resection of segment of ileum and mesentery containing mass	Not documented
11	Matsumoto *et al*[27]	77	F	Mesentery of the small intestine (near Bauhin's valve)	Abdominal mass	7 × 5.5	-	Mesenteric tumor	Resection of segment of ileum and mesentery containing mass	9 mo: Alive without recurrence
12	Present case	78	F	Mesentery of the small intestine (near Bauhin's valve)	None	3 × 1.5 × 1.5	-	Mesenteric tumor	Resection of themass	8 mo: Alive without recurrence

M: Male; F: Female.

cal resection. As shown in Table 1, most tumors were excised along with a segment of small bowel, probably because of the large tumor size and intestinal vascularity. From the viewpoint of lymph node dissection, however, recurrence in cervical lymph node was reported for retroperitoneal paraganglioma[5], neither local nor distant lymph node metastasis was reported for mesenteric paragangliomas.

With regard to malignant potential, the incidence of malignant change reportedly ranges from 14% to 50%[15,16]. In these reports, the clinical and histological distinction between benign and malignant tumors was unclear, and the definitive diagnosis of malignancy was based solely on the presence of metastases. The distinction of endocrine tumors was recently well defined according to the World Health Organization classification[17]. In particular, mitotic counts and the Ki-67 labeling index are of considerable significance in grading its malignant potential.

In the present case, the Ki-67 labeling index was low and mitoses were rare. The tumor presented as a well circumscribed mass with no metastases. The patient was considered to be at low risk of malignancy. However, in retroperitoneal paraganglioma, the 5- and 10-year disease-free survival rates were 75% and 45% even after successful resection, indicating that more than half of these patients will experience a relapse if followed long enough after resection[5]. Although recurrence of mesenteric paraganglioma has not been reported, long-term follow-up after surgical excision is likely to be necessary.

In conclusion, mesenteric paraganglioma is a very rare entity with a limited number of cases reported. Preoperative diagnosis of extra-adrenal paraganglioma in asymptomatic patients is usually difficult. Although rare, paraganglioma should be included in the preoperative differential diagnosis of solid mesenteric tumors. Even after complete resection, patients should continue to be followed up carefully.

REFERENCES

1 **Hayes WS**, Davidson AJ, Grimley PM, Hartman DS. Extraadrenal retroperitoneal paraganglioma: clinical, patholog-

ic, and CT findings. *AJR Am J Roentgenol* 1990; **155**: 1247-1250 [PMID: 2173385]
2 **Vázquez-Quintana E**, Vargas R, Pérez M, Porro R, Gómez Duarte C, Tellado M, Marcial M. Pheocromocytoma and gastrointestinal bleeding. *Am Surg* 1995; **61**: 937-939 [PMID: 7486419]
3 **Jaffer S**, Harpaz N. Mesenteric paraganglioma: a case report and review of the literature. *Arch Pathol Lab Med* 2002; **126**: 362-364 [PMID: 11860316]
4 **Lack EE**, Cubilla AL, Woodruff JM, Lieberman PH. Extra-adrenal paragangliomas of the retroperitoneum: A clinicopathologic study of 12 tumors. *Am J Surg Pathol* 1980; **4**: 109-120 [PMID: 7377461 DOI: 10.1097/00000478-198004000-00002]
5 **Sclafani LM**, Woodruff JM, Brennan MF. Extraadrenal retroperitoneal paragangliomas: natural history and response to treatment. *Surgery* 1990; **108**: 1124-1129; discussion 1129-1130 [PMID: 2174194]
6 **Cunningham SC**, Suh HS, Winter JM, Montgomery E, Schulick RD, Cameron JL, Yeo CJ. Retroperitoneal paraganglioma: single-institution experience and review of the literature. *J Gastrointest Surg* 2006; **10**: 1156-1163 [PMID: 16966036 DOI: 10.1016/j.gassur.2006.05.004]
7 **Young WF**. Paragangliomas: clinical overview. *Ann N Y Acad Sci* 2006; **1073**: 21-29 [PMID: 17102068 DOI: 10.1196/annals.1353.002]
8 **Robertson JH**, Gardner G, Cocke EW. Glomus jugulare tumors. *Clin Neurosurg* 1994; **41**: 39-61 [PMID: 7842616]
9 **Lo WW,** Solti-Bohman LG. Tumors of the temporal bone and the cerebellopontine angle. In: Som PM, Curtin HD, editors. Head and neck imaging, 3rd ed. St Louis, MO: Mosby-Year Book, 1996: 1449-534
10 **Bertherat J**, Gimenez-Roqueplo AP. New insights in the genetics of adrenocortical tumors, pheochromocytomas and paragangliomas. *Horm Metab Res* 2005; **37**: 384-390 [PMID: 16001332 DOI: 10.1055/s-2005-870156]
11 **Bhatt S**, Vanderlinde S, Farag R, Dogra VS. Pararectal paraganglioma. *Br J Radiol* 2007; **80**: e253-e256 [PMID: 17959918 DOI: 10.1259/bjr/21661275]
12 **Olsen WL**, Dillon WP, Kelly WM, Norman D, Brant-Zawadzki M, Newton TH. MR imaging of paragangliomas. *AJR Am J Roentgenol* 1987; **148**: 201-204 [PMID: 3024473]
13 **van Gils AP**, Falke TH, van Erkel AR, Arndt JW, Sandler MP, van der Mey AG, Hoogma RP. MR imaging and MIBG scintigraphy of pheochromocytomas and extraadrenal functioning paragangliomas. *Radiographics* 1991; **11**: 37-57 [PMID: 1671719]
14 **Brink I**, Schaefer O, Walz M, Neumann HP. Fluorine-18 DOPA PET imaging of paraganglioma syndrome. *Clin Nucl Med* 2006; **31**: 39-41 [PMID: 16374125]
15 **Lack EE.** Tumors of the adrenal gland and extra-adrenal paraganglia. In: Atlas of tumor Pathology, 3rd series, Fascicle19. Washington DC: Armed Forceds Institute of Pathology, 1974
16 **Linnoila RI,** Keeiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: Clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990; **21:** 1168-1180 [DOI: 10.1016/0046-8177(90)90155-X]
17 **Zheng YY**, Chen G, Zhou XG, Jin Y, Xie JL, Zhang SH, Zhang YN. [Retrospective analysis of 4 cases of the so-called blastic NK-cell lymphoma, with reference to the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues]. *Zhonghua Binglixue Zazhi* 2010; **39**: 600-605 [PMID: 21092587]
18 **Arean VM**, Ramirez DE, Arellano GA. Intra-abdominal non-chromaffin paraganglioma. *Ann Surg* 1956; **144**: 133-137 [PMID: 13327852]
19 **Carmichael JD**, Daniel WA, Lamon EW. Mesenteric chemodectoma. Report of a case. *Arch Surg* 1970; **101**: 630-631 [PMID: 4320324 DOI: 10.1001/archsurg.1970.01340290086021]
20 **Tanaka S,** Ooshita H, Kaji H. Extraadrenal paraganglioma of the mesenterium. *Rinsyo geka* 1991; **46:** 503-506
21 **Ishikura H,** Miura K, Morita J. A case of mesenteric paraganglioma. *Syokakigeka* 1996; **19:** 651-655
22 **Onoue S,** Katoh T, Chigura H, Matsuo K, Suzuki M, Shibata Y. A case of malignant paraganglioma arising in the mesentery. *J Jpn Surg Assoc* 1999; **60:** 3297-3300 [DOI: 10.3919/jjsa.60.3297]
23 **Muzaffar S**, Fatima S, Siddiqui MS, Kayani N, Pervez S, Raja AJ. Mesenteric paraganglioma. *Can J Surg* 2002; **45**: 459-460 [PMID: 12500926]
24 **Ponsky LE**, Gill IS. Laparoscopic excision of suspected extra-adrenal pheochromocytoma located in the mesenteric root. *J Endourol* 2002; **16**: 303-305 [PMID: 12184081 DOI: 10.1089/089277902760102794]
25 **Kudoh A**, Tokuhisa Y, Morita K, Hiraki S, Fukuda S, Eguchi N, Iwata T. Mesenteric paraganglioma: report of a case. *Surg Today* 2005; **35**: 594-597 [PMID: 15976959 DOI: 10.1007/s00595-004-2966-3]
26 **Nobeyama I,** Sano T, Yasuda K, Kikuchi C, Sone K, Kudo J, Oikawa M, Tamahashi N. [Case report of a paraganglioma of the mesenterium]. *Nihon Shokakibyo Gakkai Zasshi* 2004; **101:** 998-1003 [PMID: 15478664]
27 **Matsumoto K,** Hirata K, Kanemitsu S, Kawakami S, Aoki T, Nagata N, ITO H. A case of mesenteric paraganglioma. *Nihon Shokaki Geka Gakkai Zasshi* 2006; **39:** 84-89

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CASE REPORT

Pancreatic insulinoma combined with glucagon positive cell: A case report

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Abstract

We present a 70-year-old man who was referred for surgery with uncontrollable hypoglycemia. Ultrasonography and abdominal contrast computed tomography revealed a hypervascular tumor of 1 cm in diameter in the pancreatic tail. With a diagnosis of insulinoma, we performed a distal pancreatectomy. The patient showed a good postoperative course without any complications. The patient's early morning fasting hypoglycemia disappeared. The respective levels of C-peptide and insulin dropped from 14.9 ng/mL and 4860 μIU/mL preoperatively to 5.3 ng/mL and 553 μIU/mL after surgery. A histopathological examination demonstrated that the tumor was a pancreatic neuroendocrine tumor, grade 1. Immunostaining was negative for insulin and positive for CD56, chromogranin A, synaptophysin and glucagon. These findings suggested that the tumor was clinically an insulinoma but histopathologically a glucagonoma. Among all insulinoma cases reported between 1985 and 2010, only 5 cases were associated with independent glucagonoma. In this report, we characterize and discuss this rare type of insulinoma by describing the case we experienced in detail.

Key words: Hypoglycemia; Insulinoma; Pancreas; Neuroendocrine tumor; Glucagon

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INTRODUCTION

Gastrointestinal and pancreatic neuroendocrine tumors (PNETs) comprise a group of rare neoplasms arising from the neuroendocrine system of the gut. The annual incidence is estimated at 1-4 in 100 000, showing a trend toward a higher incidence over recent decades[1-5]. Advancing diagnostic techniques have enabled the early detection of both functional and nonfunctional PNETs in recent years and, as a result, these tumors are more likely to be cured by radical operation. Most of these tumors are sporadic and completely cured by enucleation, but cases of high-grade malignancy, those accompanied by independent tumor(s) that secrete other hormone(s) and those with multiple tumors require careful attention.

CASE REPORT

The case was a 70-year-old man diagnosed with diabetes mellitus 15 years prior to the current presentation who

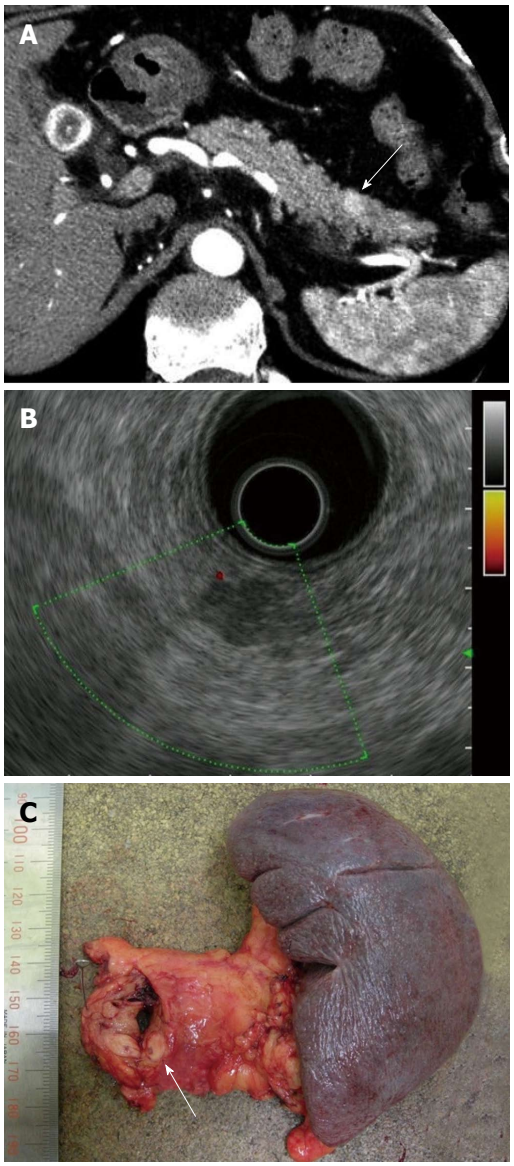

Figure 1 Removal of tumor. A: Enhanced abdominal computed tomography showed a tumor of 1 centimeter in diameter in the tail of the pancreas which was highly contrasted in the arterial phase (arrow); B: Endoscopic ultrasonography identified a uniformly hypoechoic tumor which measured 11 mm × 6 mm with a smooth surface in the tail of the pancreas; C: The resected specimen obtained from distal pancreatectomy and splenectomy included a solid whitish nodule (arrow).

was started on insulin self-injections in 2011. In 2012 he was placed under observation by the hospital due to worsening nephropathy. Two months ago, he presented with overhydration and started dialysis; he developed fasting hypoglycemia that did not improve after discontinuing the insulin injections. Careful examinations suggested that he had an insulinoma in the tail of the pancreas. He was given diazoxide and referred for surgery. The examinations on admission showed the following results: level of consciousness, lucid; blood pressure, 136/91 mmHg; pulse, 82 bpm; temperature, 36.6 ℃; overall status, stable. The patient had renal anemia and hypoalbuminemia (Table 1). The renal function test results and fasting blood glucose level before starting dialysis are shown in Table 1.

Table 1 Blood test findings on admission

Albumin, g/dL	3.0 (3.9-4.9)
Total bilirubin, mg/dL	0.3 (0.2-1.0)
Aspartate aminotransferase, IU/L	7 (10-40)
Alanine aminotransferase, IU/L	7 (5-45)
Blood urea nitrogen, mg/dL	54 (7.2-20.0)
Creatinine, mg/dL	8.2 (0.5-1.1)
Sodium, mmol/L	131 (136-145)
Potassium, mmol/L	4.1 (3.6-4.8)
Chlorine, mmol/L	101 (99-109)
White blood cell, μL	8000 (3100-9500)
Hemoglobin, g/dL	9.9 (13.5-16.9)
Platelet /μL	23.6×10^4 (15.1-34.9)
Fasting blood sugar, mg/dL	290 (70-109)
Hemoglobin A1c	7.6% (4.3%-5.8%)
Insulin, μIU/mL	4860 (1.8-12.2)
C-peptide, ng/mL	14.87 (0.61-2.09)
Binding rate of anti-insulin antibodies	76.2% (< 0.4%)
Carcinoembryonic, ng/mL	7.8 (< 5.0)
Pancreatic cancer-associated antigen-2, U/mL	190 (< 150)

Renal function test results and fasting blood glucose level before starting dialysis. Values in parentheses are normal ranges in our institution. All data were collected during the fasting state.

The blood levels of insulin and C-peptide were remarkably high, and those of carcinoembryonic antigen and duke pancreatic monoclonal antigen type 2 were slightly high. The levels of thyroid hormone and pituitary hormone were normal. The binding rate of anti-insulin antibodies was high, and we therefore could not deny insulin autoimmune syndrome.

Abdominal contrast computed tomography revealed a tumor 1 cm in diameter in the tail of the pancreas that was highly contrasted in the arterial phase (Figure 1A). The main pancreatic duct was not expanded, and the tumor was a suspected islet tumor. Endoscopic ultrasonography identified a uniformly hypoechoic tumor in the tail of the pancreas that measured 11 mm × 6 mm and had a smooth surface. Doppler ultrasonography demonstrated blood flow in the marginal regions of the tumor (Figure 1B). No other tumors were observed in the pancreas. We performed a distal pancreatectomy because intraoperative ultrasonography (IOUS) revealed that the tumor was close to the main pancreatic duct, making enucleation difficult. A cross-section of the surgical specimen showed a solid whitish nodule (Figure 1C). The tumor was preoperatively suspected as an insulinoma, but immunostaining showed that the main lesion was negative for insulin and positive for glucagon (Figure 2A and B). Additionally, the tumor was positive for CD56, chromogranin A and synaptophysin and negative for somatostatin. With an MIB-1 index of 1.6% and mild venous invasion, the tumor was identified as an NET, grade 1 (G1). At the slightly tail side of the main lesion, one hyperplastic nodule 3 mm in diameter was observed. Immunostaining demonstrated that the microadenoma was positive for insulin and glucagon (Figure 2C and D). After surgery, the blood levels of insulin and C-peptide significantly decreased, but the binding rates of anti-insulin antibodies were unchanged (Table 2). The patient resumed insulin self-injections and

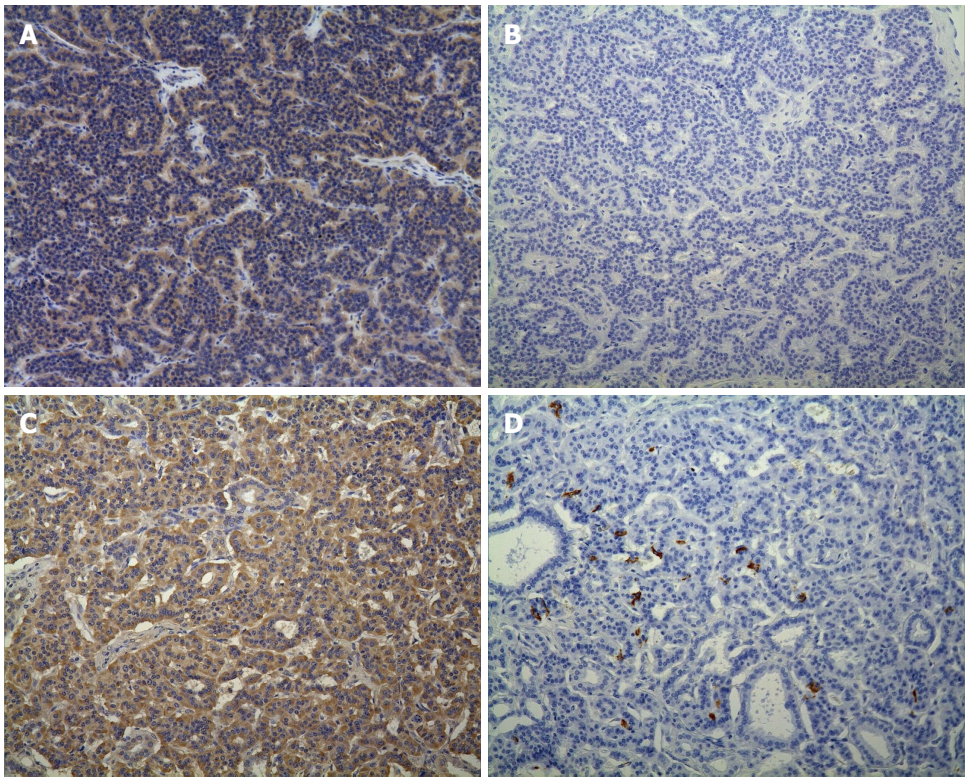

Figure 2 Immunostaining histological findings for the main lesion and the microadenoma (× 100). A: The main lesion revealed positive for glucagon; B: The main lesion revealed negative for insulin; C: The microadenoma revealed most positive for glucagon; D: The microadenoma revealed weakly positive for insulin.

Table 2 Changes of three parameters around distal pancreatectomy

	Before the operation	After the operation (POD 14)
Serum insulin level (1.8-12.2 μIU/mL)	4860	553
Serum C-peptide level (0.61-2.09 ng/mL)	14.87	5.28
Binding rate of anti-insulin antibodies (< 0.4%)	76.2	70.3

Values in parentheses are normal ranges in our institution. POD: Postoperative day.

achieved good glycemic control without taking diazoxide. He was discharged without complications on postoperative day 14.

DISCUSSION

Neuroendocrine tumors (NETs) originate from the pancreas or gastrointestinal tract and are histologically divided into NET G1, NET G2 and neuroendocrine carcinoma, including small cell type, large cell type, and mixed adenoneuroendocrine carcinoma, according to the World Health Organization classification[6]. Our case was ultimately diagnosed as an NET G1. Endocrinologically, functional tumors account for 41%-48%, and most are insulinomas[7,8]. The symptoms of insulinoma generally include hypoglycemia resulting in neuroglycopenic symptoms and hyperadrenalism because of a vicarious increase in adrenalin[9]. While blood examinations are useful for identifying insulinoma, imaging studies are helpful for localizing tumors. In recent years, surgeons have had to guess the locations of some microscopic tumors by observing the hormones flowing back to the hepatic vein after an intraarterial injection of calcium and then resecting the tumors under IOUS[10,11]. Most insulinomas are sporadic and completely cured by enucleation. After surgical therapy, patients with insulinomas generally have excellent long-term survival. A large patient cohort from the Mayo Clinic in Rochester demonstrated that cure was achieved in 98% of patients after surgical resection[12,13]. However, some cases, including high-grade malignant tumors with a poor expected prognosis, those accompanied by independent tumor(s) that secrete other hormone(s) and patients with multiple insulinomas, require careful attention[14]. Specifically, the percentage of patients with concomitant insulinoma and glucagonoma among all insulinoma cases reported in Japan between 1991 and 2000 was 1.7% (6/358)[15]. Many were mixed tumors, which can produce more than one type of hormone. Mixed endocrine pancreatic tumors producing several peptide hormones have also been reported in the West[16,17]. However, our patient had 2 independent lesions, and it is therefore highly likely that we could not achieve good glycemic control only by simple enucleation of the main lesion. To our knowledge, only 6 cases including our case, which had both insulinoma and glucagonoma, have been reported since 1985 in Japan (Table 3)[18-22]. There were no particular correlations with age or gender among the 6 patients, and in all cases, only the insulinoma was responsible for their chief complaints.

Table 3 Reports of coexistent cases of pancreatic insulinoma and glucagonoma in Japan

Case	Age (yr)	Gender	Chief compliant	Definitive diagnostic procedure	Preoperative diagnosis	Operative procedure	Postoperative diagnosis
1[18]	24	M	Consciousness disturbance	ASVS + AG	Six insulinoma at pancreatic tail	DP	Five insulinomas and two glucagonomas
2[19]	73	F	Consciousness disturbance	ASVS	One insulinoma at the region of GDA perfusion	enucleation	One insulinoma and one glucagonoma
3[20]	21	M	Consciousness disturbance	ASVS	One insulinoma at the region of SpA perfusion	1st enucleation, 2nd DP	One insulinoma and one glucagonoma
4[21]	60	F	Consciousness disturbance	AG	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
5[22]	59	F	Consciousness disturbance	CT	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
6 (our case)	70	M	Fasting hypoglycemia	CT + EUS	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma

ASVS: Arterial stimulation and venous sampling; AG: Angiography; CT: Computed tomography; EUS: Endoscopic ultrasound; GDA: Gastroduodenal artery; SpA: Splenic artery; DP: Distal pancreatectomy; M: Male; F: Female.

Glucagonoma was postoperatively diagnosed in most cases by examining additional tumors that were perioperatively identified by IOUS and resected. In 1 case (Case 3), the surgeons postoperatively identified an enucleated tumor as a glucagonoma and performed further surgery to improve persisting hypoglycemia; the patient later underwent distal pancreatectomy. Some PNETs secrete multiple hormones or are accompanied by independent hormone-positive cells that secrete other hormone(s). In this case, a small hyperplasic nodule secreting insulin incidentally coexisted with a glucagonoma. Some have reported that pancreatic islet cell hyperplasia could cause hyperinsulinemic hypoglycemia[23-27]. It is not necessarily easy to clinically and preoperatively diagnose such rare cases, even with advancing localization techniques. Careful attention is thus required to identify possible multiple lesions and monitor patients for the postoperative recurrence of tumors secreting the same or other hormone(s).

In this report, we characterized and discussed a rare insulinoma case that was preoperatively diagnosed as pancreatic insulinoma and postoperatively shown to be accompanied by glucagon-positive cells.

REFERENCES

1 **Quaedvlieg PF**, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* 2001; **12**: 1295-1300 [PMID: 11697843]

2 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959 [PMID: 12569593 DOI: 10.1002/cncr.11105]

3 **Lepage C**, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* 2004; **53**: 549-553 [PMID: 15016750 DOI: 10.1136/gut.2003.026401]

4 **Hemminki K**, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer* 2001; **92**: 2204-2210 [PMID: 11596039]

5 **Ehehalt F**, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. *Oncologist* 2009; **14**: 456-467 [PMID: 19411317 DOI: 10.1634/theoncologist.2008-0259]

6 **Rindi G**, Arnold R, Bosman FT. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of the digestive system. Lyon: IARC, 2010

7 **Pomianowska E**, Gladhaug IP, Grzyb K, Røsok BI, Edwin B, Bergestuen DS, Mathisen O. Survival following resection of pancreatic endocrine tumors: importance of R-status and the WHO and TNM classification systems. *Scand J Gastroenterol* 2010; **45**: 971-979 [PMID: 20441530 DOI: 10.3109/00365521003782363]

8 **Phan GQ**, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. *J Gastrointest Surg* 1998; **2**: 472-482 [PMID: 9843608 DOI: 10.1016/S1091-255X(98)80039-5]

9 **Norton JA**, Fang TD, Jensen RT. Surgery for gastrinoma and insulinoma in multiple endocrine neoplasia type 1. *J Natl Compr Canc Netw* 2006; **4**: 148-153 [PMID: 16451771]

10 **Baba Y**, Hayashi S, Senokuchi T, Nakajo M. Which indexes are appropriate among those derived from selective arterial calcium stimulation and venous sampling (ASVS) for diagnosing pancreatic insulinomas? Evaluation using receiver operating characteristic analyses. *Pancreas* 2011; **40**: 308-310 [PMID: 21311308 DOI: 10.1097/MPA.0b013e3181f74ac4]

11 **Haji S**, Nomura H, Yasuda K, Hashimoto N, Ohyanagi H. Combining the selective arterial calcium injection test and intraoperative blood glucose monitoring for multiple insulinomas: report of two cases. *Surg Today* 2000; **30**: 537-540 [PMID: 10883467 DOI: 10.1007/s005950070123]

12 **Grant CS**. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005; **19**: 783-798 [PMID: 16253900 DOI: 10.1016/j.bpg.2005.05.008]

13 **Service FJ**, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc* 1991; **66**: 711-719 [PMID: 1677058]

14 **de Herder WW**, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falconi M, Kwekkeboom DJ, Oberg K, Eriksson B, Wiedenmann B, Rindi G, O'Toole D, Ferone D. Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology* 2006; **84**: 183-188 [PMID: 17312378 DOI: 10.1159/000098010]

15 **Tsuzuki Y**, Ishii H. [Insulinoma--a statistical review of 358 cases of insulinoma reported from 1991 to 2000 in Japan]. *Nihon Rinsho* 2001; **59** Suppl 8: 121-131 [PMID: 11808217]

16 **Larsson LI**, Grimelius L, Håkanson R, Rehfeld JF, Stadil F, Holst J, Angervall L, Sundler F. Mixed endocrine pancreatic

tumors producing several peptide hormones. *Am J Pathol* 1975; **79**: 271-284 [PMID: 167586]
17 **Larsson LI**, Schwartz T, Lundqvist G, Chance RE, Sundler F, Rehfeld JF, Grimelius L, Fahrenkrug J, Schaffalitzky de Muckadell O, Moon N. Occurrence of human pancreatic polypeptide in pancreatic endocrine tumors. Possible implication in the watery diarrhea syndrome. *Am J Pathol* 1976; **85**: 675-684 [PMID: 998736]
18 **Sakashita F,** Osada S, Komori S, Matsui S, Tokuyama Y, Okumura N, Tanaka H, Hosono Y, Sugiyama Y, Adachi Y. A case of pancreatic insulinomas with glucagon producing tumors after enucleation for pancreatic endocrine tumor 4 years before. *Jpn J Gastroenterol Surg* 2007; **40:** 634-638
19 **Sugihara S,** Egami T, Tsurusaki S, Ayame H, Nakai K. A case of small insulinoma associated by clinically silent glucagonoma. *Jpn J Gastroenterol Surg* 1995; **28:** 2295-2298
20 **Noguchi Y,** Yoshii M, Tukaguti I. A case of MEN type 1 combined insulinoma and glucagonoma. *Rinsho Hoshasen* 1996; **41:** 385-388
21 **Miura S,** Sasakuri M, Koga M, Noda K, Deishi M. A case of insulinoma associated by glucagonoma. *Horumon To Rinsho* 1991; **39:** 152-154
22 **Kyo M,** Ichikawa Y, Nakano E. A case of metastatic renal tumor from pancreatic malignant glucagonoma combined with benign insulinoma. *Nishinihon Hinyokika* 1987; **49:** 235-240
23 **Webb GC**, Akbar MS, Zhao C, Swift HH, Steiner DF. Glucagon replacement via micro-osmotic pump corrects hypoglycemia and alpha-cell hyperplasia in prohormone convertase 2 knockout mice. *Diabetes* 2002; **51**: 398-405 [PMID: 11812747 DOI: 10.2337/diabetes.51.2.398]
24 **Zhang X**, Gaspard JP, Mizukami Y, Li J, Graeme-Cook F, Chung DC. Overexpression of cyclin D1 in pancreatic beta-cells in vivo results in islet hyperplasia without hypoglycemia. *Diabetes* 2005; **54**: 712-719 [PMID: 15734847 DOI: 10.2337/diabetes.54.3.712]
25 **Sun L**, Eklund EA, Chung WK, Wang C, Cohen J, Freeze HH. Congenital disorder of glycosylation id presenting with hyperinsulinemic hypoglycemia and islet cell hyperplasia. *J Clin Endocrinol Metab* 2005; **90**: 4371-4375 [PMID: 15840742 DOI: 10.1210/jc.2005-0250]
26 **Meier JJ**, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. *Diabetes Care* 2006; **29**: 1554-1559 [PMID: 16801578 DOI: 10.2337/dc06-0392]
27 **Escribano O**, Guillén C, Nevado C, Gómez-Hernández A, Kahn CR, Benito M. Beta-Cell hyperplasia induced by hepatic insulin resistance: role of a liver-pancreas endocrine axis through insulin receptor A isoform. *Diabetes* 2009; **58**: 820-828 [PMID: 19136656 DOI: 10.2337/db08-0551]

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In press

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Organization as author

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Both personal authors and an organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

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Conference proceedings

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Conference paper

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Electronic journal (list all authors)

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

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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