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Abdominal contamination with *Candida albicans* after pancreaticoduodenectomy is related to hemorrhage associated with pancreatic fistulas

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ABSTRACT

Background/Objectives: Pancreatic fistulas are one of the most frequent morbidities after pancreaticoduodenectomy. Several reports have suggested a relationship between bacterial infections and postoperative pancreatic fistulas, although details of the mechanisms involved in hemorrhage in association with the fistulas have not been elucidated. This study retrospectively examined the relationship between positive drainage culture and hemorrhage associated with pancreatic fistulas after pancreaticoduodenectomy.

Methods: From January 2012 to December 2015, 142 consecutive patients underwent pancreaticoduodenectomy at our institution. We retrospectively reviewed the patients' demographic data, perioperative laboratory data, and drainage culture results.

Results: Twenty-four (17%) patients had clinically relevant postoperative pancreatic fistulas, whereas thirty-four (24%) patients experienced positive drainage culture. Multivariable analysis revealed that positive drainage culture was independently associated with clinically relevant postoperative pancreatic fistulas (odds ratio, 18.1; 95% confidence interval, 5.5–72.2; $P < 0.001$). Additionally, the prevalence of *Candida albicans* in the lavage of eight patients significantly correlated with hemorrhage associated with pancreatic fistulas (odds ratio, 43.5; 95% confidence interval, 6.2–513.3; $P < 0.001$). Seventy-five percent (6/8) of these patients suffered potentially lethal hemorrhagic complications and needed intervention.

Conclusions: A positive abdominal drainage culture is associated with the development of pancreatic fistulas. Moreover, the presence of *Candida albicans* in drainage fluid may be a risk factor for hemorrhagic complications.

Introduction

Complete resection with pancreaticoduodenectomy (PD) is essential for long-term survival in patients with periampullary malignancies. Although 70 years have passed since Whipple popularized PD as an effective therapeutic option [1], PD is still one of the most difficult operations of the alimentary tract. Recently, the mortality rate following PD has decreased to as low as 3% in specialized centers in Asia [2–4]. However, its morbidity rate has stayed at approximately 40% over the past decades, despite the many efforts [4,5].

The most challenging complication after PD is a postoperative pancreatic fistula (POPF), which sometimes results in lethal conditions, such as hemorrhage or abdominal sepsis. Several factors have been reported to be associated with the occurrence of POPFs [2,6–11]. In addition, some investigators have recently attributed the development of POPFs to the presence of abdominal infections [12,13]. However, the pathogenesis and etiology underlying hemorrhage in association with POPFs in the presence of infections have not been elucidated.

In this study, we aimed to identify the relationship between the results of drainage culture tests after PD and POPFs. Positive drainage culture was independently associated with CR-POPF. In addition, we found an association between hemorrhage after POPFs and abdominal C. albicans infection. This study provides insights

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into the management of patients after PD.

Materials and methods

Patients

From January 2012 to December 2015, 142 consecutive patients at Kyoto University Hospital (Kyoto, Japan) underwent PD and were enrolled in this retrospective study. The patients were divided into two groups to reveal the risk factors for clinically relevant (CR)-POPFs: CR-POPF and non-CR-POPF groups. According to the criteria of the International Study Group on Pancreatic Fistula (ISGPF), POPF was defined as a three-fold increase in amylase in the drainage fluid relative to the upper limit of serum amylase at our institution on and after postoperative day (POD) 3 [14]. Grades A, B, and C POPFs were determined according to the ISGPF criteria. We did not include patients with grade A POPF in the CR-POPF group, because grade A POPFs are not thought to be clinically significant since fistulas of this degree of severity have no clinical impact [15].

Data on patients' background (age, sex, past history, and Brinkman index), body mass index (BMI), perioperative laboratory data, disease pathology, and operation-related factors were retrospectively collected from their medical records. This study was approved by the Ethics Committee of Kyoto University and was conducted in accordance with the Declaration of Helsinki (2008). Written informed consent for study participation was obtained from all patients prior to the operation.

Operative procedures

Resection was performed using any of the classic methods depending on the extent of the disease: PD, pylorus-preserving PD (PPPD), or subtotal stomach-preserving PD (SSPPD). Briefly, after dissection of the mesenteric lymph nodes, Kocher's mobilization, and dissection of the hepatoduodenal ligament, the pancreas was anteriorly divided using an electric scalpel. Remnant tissue, including the pancreatic head plexus, was resected, and preparations were made for anastomosis, such as mobilization of the edge of the pancreas. If the portal vein or superior mesenteric vein was invaded by the lesion, combined resection of the vessels and vascular reconstruction prior to the anastomosis were performed.

All pancreatic anastomoses to the alimentary tract were accomplished using end-to-side pancreaticojejunostomy. The pancreatic duct was connected to the jejunum by 12 interrupted sutures using 6-0 PDS-II (Johnson & Johnson, New Brunswick, NJ, USA) with a detaining external stenting tube (Sumitomo Bakelite Co., Ltd., Tokyo, Japan). The stump of the pancreatic parenchyma was attached to the outer jejunal wall by Kakita's method or the modified Blumgart procedure using 3-0 PDS-II (Johnson & Johnson) [16,17]. Next, choledochojejunostomy and antecolic reconstruction of the alimentary tract were performed. Two closed suction drainage tubes (J-VAC drainage system, Johnson & Johnson) were placed behind the choledochojejunostomy and the pancreaticojejunostomy.

Perioperative management

Flomoxef sodium (1 g) was intravenously administered 30 min preoperatively and every 3 hourly during the operation as prophylactic antibiotic cover. The same antibiotic was continued twice a day for 5 days after PD. Prophylactic octreotide was not used during the study period. If a patient showed symptoms suggestive of systemic inflammatory response syndrome [18], empiric antibiotic therapy using carbapenem or piperacillin/tazobactam was initiated after appropriate culture tests. De-escalation of these antibiotics was considered according to the improvement in clinical symptoms or laboratory tests.

Routine blood tests were performed preoperatively and on POD 1, 2, 3, 5, and 7. Amylase levels in the drainage fluid were measured and drainage culture was performed on POD 1, 3, 5, and 7. Drainage fluid collected in the bag was discarded in a sterile manner by a nurse every 6 h, while monitoring the characteristics and volume of the fluid. Removal of the drainage tubes was considered depending on the POPF status and whether clinical symptoms or laboratory data indicated that inflammation had improved. Additional culture tests were performed in necessary if the patients showed signs of infection. For hemorrhagic complications, transarterial embolization or a reoperation was performed as soon as possible.

Statistical analysis

Continuous variables are indicated as median (range). Comparisons between the CR-POPF and non-CR-POPF groups were made using the Mann–Whitney *U* test or chi-square test when appropriate. JMP 5.0 software (SAS Institute, Inc., Cary, NC, USA) was used for analysis. Multiple logistic regression analysis was performed using factors selected by univariate analysis ($p < 0.05$) as being significant. Categorical variables in small sample size analyses were compared using Fisher's exact test. Values of $p < 0.05$ were considered statistically significant.

Results

Comparison of backgrounds between the CR-POPF and non-CR-POPF groups

Of the 142 consecutive patients, POPFs (Grades A to C) occurred in 32 (23%) patients, while CR-POPF occurred in 24 (17%) patients (Grade B: 15, and Grade C: 9). The 30-day mortality rate was 1.4%.

We performed an analysis to determine factors associated with CR-POPF (Table 1). Evaluation revealed that the patients' backgrounds, including age, sex, presence of diabetes, past abdominal surgery, cardiovascular disease, BMI, prevalence of preoperative biliary drainage, and Brinkman index, were not statistically significantly different between the CR-POPF and non-CR-POPF groups (Table 1).

The prevalence of a preoperative estimated glomerular filtration rate (eGFR) of ≤55 mL/min was not significantly different between the groups (CR-POPF: 4/24: 17%, non-CR-POPF: 12/118: 10%, $p = 0.381$), and no patient on chronic hemodialysis was included in either group. Other laboratory data were not statistically significantly different between the two groups (data not shown).

Univariate and multivariable analysis of factors associated with CR-POPF

Operation-related factors in the two groups are presented in Table 2. The prevalence of pancreatic cancer was significantly higher in the non-CR-POPF group (CR-POPF: 7/24: 29%, non-CR-POPF: 67/118: 57%; $p = 0.013$). The method of resection (PD, PPPD, or SSPPD), incidence of vascular reconstruction, method used for pancreaticojejunostomy (Kakita or modified Blumgart), operative time, and intraoperative blood loss were not significantly different between the two groups. Both pancreatic duct diameter of ≤3 mm (CR-POPF: 17/24: 71%, non-CR-POPF: 49/118: 42%; $p = 0.008$) and the rate of soft-textured pancreas (CR-POPF: 15/24: 63%, non-CR-POPF: 39/118: 33%; $p = 0.008$) were statistically significant risk factors for POPFs on univariate analysis. Additionally, the median drain amylase level on POD1 in the CR-POPF group was significantly higher than that in the non-CR-POPF group (1043 IU/L

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