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Stent-induced symptomatic pancreatic duct stricture after endoscopic prophylactic pancreatic duct stent placement for the normal pancreas

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ABSTRACT

Background/Objectives: Stent-induced pancreatic duct stricture (SI-PDS) is a complication associated with pancreatic stent placement. However, symptomatic SI-PDS associated with prophylactic pancreatic duct stents has not been sufficiently investigated.

Methods: We examined the incidence and characteristics of symptomatic SI-PDS in patients who underwent pancreatic duct stent placement to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) between April 2007 and March 2017.

Results: We examined 124 patients with normal pancreases consisting of 75 men and 49 women with a median age of 67.5 years [interquartile range (IQR): 61–74 years]. The median main pancreatic duct (MPD) diameter was 3.3 mm (IQR: 2.6–4.1 mm). The median duration of stent placement was 7 days (IQR: 3–14 days). Spontaneous dislodgment stents were placed in 43.5% of cases (54/124). The diameter of the stent was 5 Fr in 93.5% of cases (116/124) and 7 Fr in 6.5% of cases (8/124). Symptomatic SI-PDS was observed in 2.4% (3/124) of patients overall: 6.5% of patients with an MPD diameter of <3 mm and 0% of patients with an MPD diameter of ≥3 mm. Univariate analysis revealed that an MPD diameter <3 mm was a significant factor for symptomatic SI-PDS ($p = 0.048$). All cases of symptomatic SI-PDS improved with endoscopic treatment.

Conclusions: Symptomatic SI-PDS occurred in 2.4% of patients who underwent prophylactic pancreatic duct stent placement for normal pancreases. Patients with an MPD diameter of <3 mm may be susceptible to symptomatic SI-PDS.

Introduction

Pancreatic duct stents are used to treat pancreatic duct strictures, pancreatic pseudocysts, and pancreatic duct injury, and to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) (in patients at high risk for PEP, such as cases of difficult biliary cannulation, post-endoscopic papillectomy, etc.). Several studies have investigated the efficacy of pancreatic duct stent placement [1–6].

Complications associated with pancreatic duct stent placement include bleeding, duodenal erosion, duct perforation, infection, pain/pancreatitis due to stent occlusion, pseudocyst, perforation (intestinal/retroperitoneal), and stent migration [5,7]. Additionally, stent-induced pancreatic duct stricture (SI-PDS) is a complication of pancreatic duct stent placement [6–10].

Pancreatic duct stent placement has recently been proven to be effective in preventing PEP and is recommended for patients at high risk for PEP [2–5]. Although the placement of a plastic stent is reported to cause pancreatic ductal and parenchymal changes in 24–80.3% of cases [8–10,12], prophylactic pancreatic duct stent placement results in complications in only 4.4% of cases [5]. Thus, almost all cases involving prophylactic stent placement are asymptomatic, even when pancreatic ductal and parenchymal changes occur. There are eight reported cases of symptomatic SI-PDS in previously normal pancreatic ducts resulting from therapeutic pancreatic duct stent placement [11]. However, very little is known about the incidence or characteristics of symptomatic SI-PDS resulting from prophylactic pancreatic duct stent placement.

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Therefore, we retrospectively examined the incidence and characteristics of symptomatic SI-PDS in cases of pancreatic duct stent placement with the aim of preventing PEP in normal pancreases.

Methods

The current study utilized the Kitasato University Hospital Endoscopy Database. Of 318 patients who underwent pancreatic duct stent placement between April 1, 2007 and March 31, 2017, we selected patients who underwent pancreatic duct stent placement to prevent pancreatitis in normal pancreases and who underwent follow-up for at least 1 year as subjects for the present study. Health conditions were confirmed by telephone for patients who discontinued follow-up or transferred to other hospitals within 1 year. All patients provided written informed consent prior to the procedure.

A normal pancreas was defined as a pancreas in which ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI) conducted prior to stent placement did not show enlargement, atrophy, pancreatic stones, cystic lesions, pancreatic tumor, or pancreatic duct dilatation. The absence of pancreatic duct dilatation was defined as a main pancreatic duct (MPD) diameter $\leq$ 5 mm (assessed with endoscopic retrograde pancreatography), the absence of an irregular width, and the absence of branch duct dilatation. The ends of the stent were placed in the head and body of the pancreas along the course of the pancreatic duct to avoid stent kinking.

Stent-induced pancreatic duct stricture was defined as pancreatic duct stricture in the stent placement site for which diagnostic imaging (ultrasonography, CT, MRI) and pancreatic juice cytology ruled out malignant disease. Pancreatic duct stricture was diagnosed as symptomatic if the patient demonstrated abdominal symptoms and elevated pancreatic enzymes ($\geq$3 times the upper limit of the normal range) or pancreatitis on imaging.

We retrospectively examined age, sex, MPD diameter, stent characteristics, duration of stent placement, and the occurrence of PEP. The MPD diameter was defined as the maximum diameter downstream from the end of the stent. Diagnoses of PEP and assessments of its severity were based on the American Society for Gastrointestinal Endoscopy severity grading system [13]. This study was approved by the institutional review board of Kitasato University Hospital and conformed to the Declaration of Helsinki guidelines (as revised in Fortaleza, Brazil, October 2013).

Endoscope and instruments

In the present study, we used a duodenoscope (TJF-260V, JF-260V, Olympus Medical Systems, Tokyo, Japan). The pancreatic duct stents were Geenen® Pancreatic Stent Sets (with a flanged inner end, straight, Cook Medical, Bloomington, United States), while the pancreatic spontaneous dislodgement stents (PSDS) were Zimmon® Pancreatic Stent Sets with No Flap (5 Fr, 4 cm, single pigtail with an unflanged inner end, Cook Medical).

The guidewires used in the present study were Jagwire™ (Boston Scientific, Marlborough, MA, United States) and Visiglide2™ (G-260-2545A, Olympus Medical Systems).

Statistical analysis

Categorical variables were analyzed using Fisher's exact test. P values of <0.05 were considered to indicate statistical significance. Statistical analysis was performed using BellCurve for Excel version 2.00 (Social Survey Research Information Co., Ltd., Japan).

Results

The study included 124 patients (Fig. 1), consisting of 75 men and 49 women with a median age of 67.5 years [interquartile range (IQR): 60.75–74 years]. The median pancreatic duct diameter was 3.3 mm (IQR: 2.6–4.1 mm). Straight stents with a flanged inner end and PSDS with an unflanged inner end were used for 70 patients (56.5%) and 54 patients (43.5%), respectively. Stent diameter was 5 Fr for 116 patients (93.5%) and 7 Fr for 8 patients (6.5%). The median duration of stent placement was 7 days (IQR: 3–14 days). The median follow-up duration was 3.2 years (IQR: 1.6–5.4). The details of patient characteristics are shown in Table 1.

Symptomatic SI-PDS was observed in 3 patients (2.4%) overall: 6.5% of patients (3/46) with an MPD diameter of <3 mm and 0% of patients (0/78) with an MPD diameter of $\geq$3 mm. Univariate analysis revealed that symptomatic SI-PDS was significantly associated with an MPD diameter of <3 mm ($p = 0.048$). The incidence of

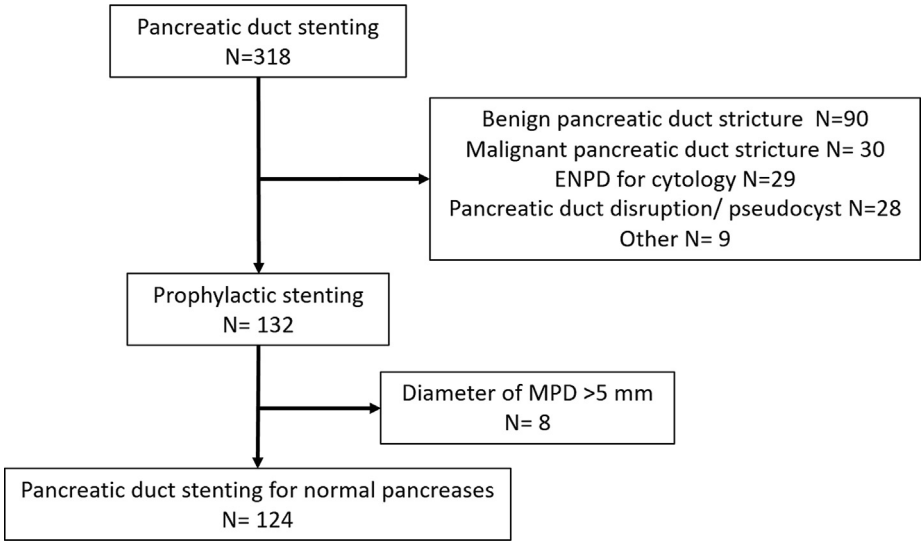

Fig. 1. Flowchart of patient enrollment.
ENPD: endoscopic nasopancreatic drainage, MPD: main pancreatic duct.

Table 1
Patient characteristics.

	N = 124
Sex male/female	75/49
Age median (IQR), yrs	67.5 (60.75–74)
Reasons for ERCP, n (%)	
Bile duct stone	33 (26.5)
Biliary drainage	
for malignant obstruction	26 (21)
for benign obstruction	5 (4)
Pancreatobiliary maljunction	3 (2.5)
Sphincter of Oddi dysfunction	2 (1.5)
Tumor of duodenal papilla	48 (39)
Others	7 (5.5)
Diameter of main pancreatic duct, median (IQR), mm	3.3 (2.6–4.1)
Type of stent, n (%)	
straight stent with a flanged inner end	70 (56.5)
spontaneous dislodgement stent with an unflanged inner end	54 (43.5)
Diameter of stent, n (%)	
5 French	116 (93.5)
7 French	8 (6.5)
Length of stent (cm)	
3	16 (13)
4	57 (46)
5	36 (29)
7	14 (11.2)
9	1 (0.8)
Duration of stent placement, median (IQR), days	7 (3–14)
Duration of follow-up, median (IQR), years	3.2 (1.6–5.4)

ERCP: endoscopic retrograde cholangiopancreatography, IQR: interquartile range.

symptomatic SI-PDS did not differ significantly based on age, sex, type of stent inner end, stent diameter, stent length, duration of stent placement, or occurrence of PEP (Table 2). The details of the three cases of SI-PDS are shown in Table 3 and in Figs. 2–4. Case 1 developed mild PEP. However, PDS occurred only at the point where the tip of the stent was deployed. Therefore, we diagnosed this case as SI-PDS and not pancreatitis-induced PDS.

Discussion

In the present study, we observed symptomatic SI-PDS in 2.4% of the cases of pancreatic duct stent placement for normal pancreases. All occurrences of SI-PDS were in patients with an MPD diameter of <3 mm.

Pancreatic duct stent placement is performed for variety of purposes and reported to be an effective procedure [1]. However, placement of 5 to 7-Fr stents results in pancreatic ductal changes in 36–80% of cases[8–10, 12] and pancreatic parenchymal changes in 68% of cases [9]. Potential mechanisms of these changes include local pancreatitis caused by the stent, direct trauma to the pancreatic duct epithelium caused by pressure or foreign material phenomenon, and occlusion of branch ducts [8,9]. These changes are reported to result in histologically irreversible fibrosis [14]. Pancreatic duct and parenchymal changes occasionally result in chronic pancreatitis as well, for which treatment is burdensome [8–12]. In some cases, endoscopic therapy fails to result in improvement, necessitating surgical treatment [11]. Therefore, measures to prevent SI-PDS are necessary.

In one study, stent-induced ductal changes occurred in 24% of cases involving a 3 to 4-Fr stent and in 80% of cases involving a 5 to 6-Fr stent [12]; while in another study, stent-induced ductal changes did not occur in cases involving a 3-Fr PSDS [15]. The reason why a small-caliber stent reduces the stent-induced ductal change may be that a smaller stent diameter leaves a greater amount of space between the stent and the ductal wall; thereby,

Table 2
Factors of symptomatic stent-induced pancreatic duct stricture.

	Age/Sex	Primary disease	Reasons for pancreatic stent	Diameter of MPD	Type of stent	Diameter and length of stent	PEP (severity)	Duration of stent placement	Symptom	Onset of symptomatic SI-PDS from stent removal	Stricture part of pancreas	Treatment and outcome
Case 1.	53/F	Bile duct stone	Difficult to bile duct cannulation	2.2 mm	PSDS with unflanged inner end	5 Fr/4 cm	Yes (mild)	Within 2 days	Pancreatitis	50 days	Head	Pancreatic stent (7 Fr, 6 months) /improvement
Case 2.	54/F	Adenoma of the duodenal papilla	Post endoscopic papillectomy	2.7 mm	Non-PSDS with flanged inner end	5 Fr/5 cm	No	12 days	Abdominal pain and elevation of pancreatic enzymes	70 days	Head	Pancreatic stent (5–10 Fr, 39 months) /improvement
Case 3.	67/F	Adenoma of the duodenal papilla	Post-endoscopic papillectomy	2.6 mm	Non-PSDS with flanged inner end	5 Fr/5 cm	No	14 days	Pancreatitis	49 days	Head	Pancreatic stent (7 Fr, 8 months) /improvement

MPD: main pancreatic duct; SI-PDS: stent-induced pancreatic duct stricture; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; PSDS: pancreatic spontaneous dislodgement stents.

Table 3
Details of the three cases of symptomatic stent-induced pancreatic duct stricture.

	Rate of symptomatic SI-PDS	p-value
All cases	2.4% (3/124)	–
Sex		
Male	0% (0/75)	0.059
Female	6.1% (3/49)	
Age, years		
>65	4% (2/50)	0.356
≤65	1.4% (1/74)	
Diameter of main pancreatic duct		
<3 mm	6.5% (3/46)	0.048
≥3 mm	0% (0/78)	
Type of inner end of stent		
with a flanged inner end	2.9% (2/70)	0.597
with an unflanged inner end	1.9% (1/54)	
Diameter of stent		
5 French	2.6% (3/116)	0.817
7 French	0% (0/8)	
Length of stent		
≤4 cm	1.4% (1/73)	0.376
≥5 cm	3.9% (2/51)	
Duration of stent placement		
≤7 days	1.4% (1/74)	0.356
≥8 days	4% (2/50)	
PEP		
Yes	5.6% (1/18)	0.378
No	1.9% (2/104)	

SI-PDS: stent-induced pancreatic duct stricture; PEP: post-endoscopic retrograde cholangiopancreatography pancreatitis; PSDS: pancreatic spontaneous dislodgement stent.

making local pancreatitis and direct trauma less likely to occur. This mechanism may also explain why symptomatic SI-PDS occurred more frequent in patients with an MPD diameter of <3 mm in our study. With a stent of the same diameter, a smaller MPD diameter would leave less space between the stent and the ductal wall, making the patient more susceptible to local pancreatitis and direct trauma, thus increasing SI-PDS. Furthermore, it was reported that small-caliber stents do not increase the incidence of PEP [12]. Therefore, to prevent SI-PDS, it is ideal that stent diameter be as small as possible. The drawback of this, however, is that inserting a 3-Fr stent requires a thin guidewire (0.018 inches); considering that treatment will primarily involve bile duct stone removal and bile duct drainage, two guidewires are required. Our results suggest that a small-caliber stent (3-Fr) should be proactively used for patients with a MPD diameter of <3 mm.

Differences in stent length have been reported to yield no differences in the incidence of stent-induced ductal changes [10]. Our study also found no differences in the incidence of symptomatic SI-PDS based on stent length. However, considering the mechanism of onset of stent-induced ductal change, trauma caused by pressure or foreign material phenomenon and branch duct occlusion should be avoided as much as possible. Thus, the placement of a short stent may prevent stent-induced ductal changes and ultimately prevent symptomatic SI-PDS. However, kinking of the stent inner end towards the pancreatic duct may increase the risk of SI-PDS. Therefore, stent length should be determined according to the course of the pancreatic duct. Particular caution is required regarding the bend of the neck of the pancreas, where stent kinking occurs easily.

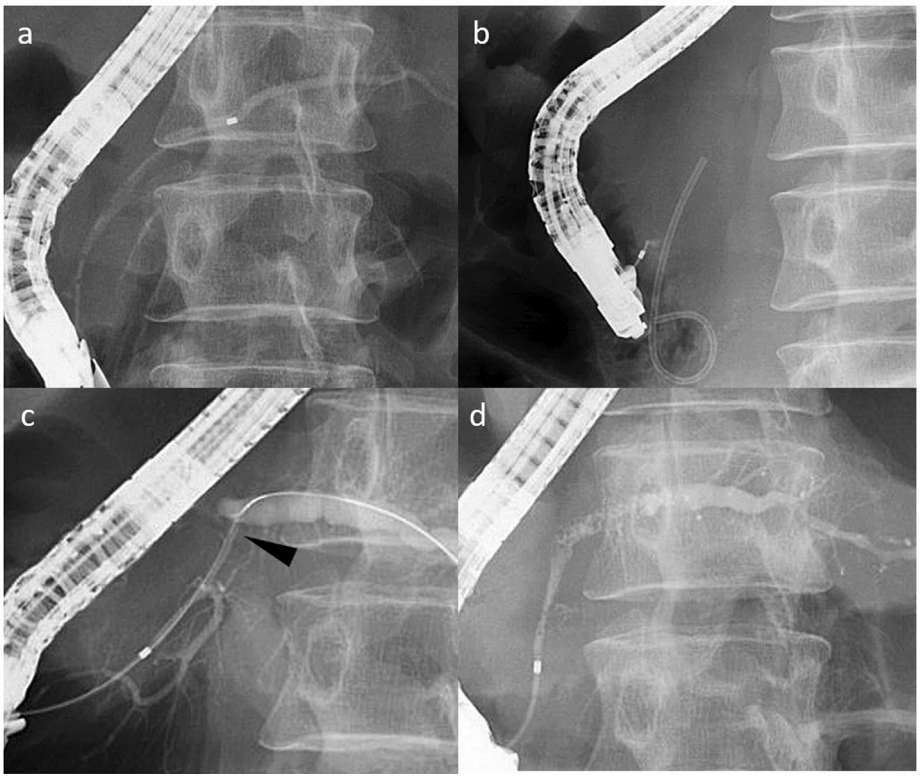

Fig. 2. Case 1: Prophylactic PSDS placement for difficult biliary cannulation.
a: endoscopic retrograde pancreatography prior to pancreatic duct stent placement.
b: post-PSDS placement (5 Fr; 4 cm; straight, unflanged stent; spontaneous dislodgement within 2 days).
c: At 50 days after PSDS dislodgement, the patient demonstrated abdominal pain and elevated pancreatic enzymes, which suggested pancreatitis due to pancreatic duct stricture. Endoscopic retrograde pancreatography revealed a stricture where the end of the PSDS was placed (black arrowhead). Dilatation of the main pancreatic duct and the branch ducts was observed upstream from this site.
d: Placement of a 7-Fr pancreatic duct stent for 6 months improved the stricture and pancreatitis. However, the dilatation of the distal pancreatic duct was irreversible.

Fig. 3. Case 2: Post-endoscopic papillectomy prophylactic pancreatic duct stent placement.
a: Pre-endoscopic papillectomy endoscopic retrograde cholangiopancreatography.
b: Placement of a biliary and pancreatic duct stent (5 Fr, 5 cm, straight, flanged stent) to prevent post-endoscopic papillectomy pancreatitis and biliary stricture. The stents were removed 12 days later.
c: At 70 days after pancreatic duct stent removal, the patient demonstrated abdominal pain and elevated pancreatic enzymes, suggesting pancreatic duct stricture. Endoscopic retrograde pancreatography revealed a pancreatic duct stricture where the tip of the stent was placed (black arrowhead), as well as slight dilatation of the distal pancreatic duct. d: Placement of a 7 to 10-Fr pancreatic duct stent for 39 months improved the stricture and pancreatic enzyme elevation. However, the pancreatic duct dilatation was irreversible.

With respect to stent shape, we observed no significant differences in the incidence of symptomatic SI-PDS between flanged and unflanged stents. However, case 3 demonstrated SI-PDS in the flap site. Therefore, unflanged stents should be used if possible. In a canine model, stent-induced ductal changes were less frequent with a wing stent designed to prevent branch duct occlusion than with a conventional stent with a side hole [16]. Stents themselves are considered to have room for improvement. One example of a better stent is a soft and flexible stent which follows the course of the pancreatic duct and is designed to prevent the occlusion of the branch ducts.

Regarding duration of stent placement, stent-induced ductal changes are reportedly triggered when a stent is left in place even for only one week [16]. According to another study, stent-induced ductal changes occur more frequently the longer the stent is left in place [10]. Therefore, it is ideal to leave the stent in place for as short as possible. For PSDS, the ideal stent is one that prevents PEP and dislodges spontaneously within a short period of time. However, in case 1 in our study, despite the PSDS dislodging within 2 days, symptomatic SI-PDS was observed 50 days later. As this case shows, shortening the duration of stent placement, by itself, may not be sufficient to prevent symptomatic SI-PDS. However, a study using a canine model reported that the severity of fibrosis increases in proportion to the duration of stent placement [14]. Even if SI-PDS develops, it may become asymptomatic if the duration of stent placement is short and fibrosis is mild. Moreover, even if SI-PDS is symptomatic, the milder the fibrosis, the more endoscopic treatment likely to improve the chances of successful dilation of the stricture. Therefore, we believe that the duration of stent placement should be short. The characteristics of an ideal stent to reduce SI-PDS are listed in Table 4.

All three cases of symptomatic SI-PDS in our study occurred in women. Although the differences between sexes in our study were not significant ($p = 0.059$), in another study of eight cases of symptomatic SI-PDS in previously normal pancreatic ducts, seven cases occurred in women [11]. Based on this study and our own results, women may be more susceptible to symptomatic SI-PDS. Due to the scarcity of reports of symptomatic SI-PDS in normal pancreases, multicenter studies should be conducted in the future.

Limitation of our study is that it was a retrospective single-center study with a small sample size. Furthermore, while univariate analysis revealed that symptomatic SI-PDS was significantly associated with an MPD diameter of <3 mm, the small number of cases of SI-PDS may reduce the statistical significance of this result. Therefore, multicenter studies with large sample sizes should be conducted in the future.

Conclusion

Prophylactic pancreatic duct stent placement for normal pancreases resulted in symptomatic SI-PDS in 2.4% of cases. Patients with an MPD diameter of <3 mm were shown to be more

Fig. 4. Case 3: Post-endoscopic papillectomy prophylactic pancreatic duct stent placement.
a: Pre-endoscopic papillectomy endoscopic retrograde pancreatography.
b: Placement of a biliary and pancreatic duct stent (5 Fr, 5 cm, straight, flanged stent) to prevent post-endoscopic papillectomy pancreatitis and biliary stricture. The stents were removed 14 days later.
c: At 49 days after pancreatic duct stent removal, the patient demonstrated pancreatitis, suggesting a pancreatic duct stricture. Endoscopic retrograde pancreatography revealed a pancreatic duct stricture where the tip of the stent was placed (black arrowhead), as well as a pancreatic duct stricture at the site of the stent flap (white arrowhead).
d: Placement of a 7-Fr pancreatic duct stent for 8 months improved the stricture. The patient did not demonstrate pancreatitis following stent removal.

Table 4
Ideal stent to reduce SI-PDS.

	characteristics of stent
Diameter of stent	· small-caliber stent (to reduce direct trauma and branch duct occlusion)
Length of stent	· variable (length to avoid kinking) · short stent (if possible, to reduce branch duct occlusion)
Shape of stent	· unflanged type (to reduce direct trauma) · many sidehole (to reduce branch duct occlusion) · wing stent (to reduce branch duct occlusion, 16)
Material of stent	· soft and flexible (to reduce direct trauma and kinking)
Duration of stent	· spontaneous dislodgement within a short period (to decrease the severity of fibrosis)

SI-PDS: stent-induced pancreatic duct stricture.

susceptible to symptomatic SI-PDS. To prevent symptomatic SI-PDS, it may be necessary to take measures such as using a small-caliber stent, using an unflanged stent, and leaving the stent in place for only a short time.

Conflicts of interests

The authors have no conflicts of interest to declare.

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