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Predictive factors for pancreatitis and cholecystitis in endoscopic covered metal stenting for distal malignant biliary obstruction

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Abstract

Background and Aim: Pancreatitis and cholecystitis are major complications after self-expandable metal stent (SEMS) placement in distal malignant biliary obstruction. We aimed to clarify predictive factors for pancreatitis and cholecystitis after covered SEMS placement.

Methods: We retrospectively reviewed 74 consecutive patients with distal malignant biliary obstruction who underwent initial endoscopic drainage using covered SEMS. Predictive factors for pancreatitis and cholecystitis were evaluated in the 74 patients described above and in 66 patients who had not undergone cholecystectomy.

Results: The incidences of pancreatitis and cholecystitis were 10.8% (8/74) and 6.1% (4/66), respectively. Univariate analysis revealed that non-pancreatic cancer ($P = 0.018$) and contrast injection into the pancreatic duct ($P = 0.030$) were significant predictive factors for pancreatitis. Multivariate analysis revealed that non-pancreatic cancer (odds ratio [OR], 4.21; 95% confidence interval [CI], 1.63–14.18; $P = 0.007$) and contrast injection into the pancreatic duct (OR, 3.34; 95% CI, 1.33–9.60; $P = 0.016$) were significant independent predictive factors for pancreatitis. On the other hand, univariate and multivariate analyses revealed that tumor involvement to the orifice of the cystic duct (OCD) was a significant independent predictive factor for cholecystitis (OR, 5.85; 95% CI, 1.91–27.74; $P = 0.005$).

Conclusions: Non-pancreatic cancer and contrast injection into the pancreatic duct were predictive factors for pancreatitis, and tumor involvement to the OCD was a positive predictive factor for cholecystitis after endoscopic covered SEMS placement for distal malignant biliary obstruction.

Introduction

Endoscopic biliary drainage with a covered self-expandable metal stent (SEMS) is an accepted form of palliative therapy for distal malignant biliary obstruction (MBO) because of its low invasiveness and long-term patency. Covered SEMSs have a significantly longer patency than uncovered SEMSs in patients with MBO, because covered SEMSs can prevent tumor ingrowth.[1,2] Furthermore, an advantage of covered SEMSs over uncovered SEMSs is that covered SEMSs can be removed endoscopically. Therefore, we usually use covered SEMSs for therapy of distal MBO. The long stent patency of covered SEMSs is important for patients with distal MBO. However, complications after covered SEMS placement are also important because these complications may necessitate additional endoscopic or surgical interventions, which may decrease the patient's quality of life or result in discontinuance of chemotherapy.

Complications of covered SEMSs include stent occlusion, migration, kinking, non-occlusion cholangitis, liver abscess, pancreatitis, and cholecystitis. A recent meta-analysis reported that stent migration, tumor overgrowth, and sludge formation were significantly higher with covered SEMSs than with uncovered SEMSs.[1] Covered SEMSs have the risk of obstruction of the main pancreatic duct or the orifice of the cystic duct (OCD) because of the covering material. Several risk factors of pancreatitis and cholecystitis after SEMS placement for distal MBO have been reported.[3–7] However, because the predictive factors for pancreatitis and cholecystitis have been the subject of few reports, the association between SEMS placement and these complications have not been completely elucidated. Thus, the predictive

factors of these complications after SEMS placement must be clarified.

On the basis of this background, the purpose of this retrospective study was to clarify the predictive factors for pancreatitis and cholecystitis in patients with distal MBO after covered SEMS placement.

Methods

Patients. We consecutively enrolled 74 patients with distal MBO who received covered SEMS placement at the Nagoya City University Graduate School of Medical Sciences between 2004 and 2011. Transpapillary initial SEMS placements were included in this study. The diagnosis of MBO was based on imaging and/or pathological findings. Malignancy was proved by histopathological confirmation obtained by endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA), bile duct biopsy (cytology), pancreatic duct cytology, or liver biopsy. These cases were judged as unresectable according to advanced tumor extension or factors regarding the conditions of these patients. Some patients received chemotherapy after SEMS placement. Laboratory data were evaluated every month after SEMS placement. Radiological examinations were performed at fixed intervals or if stent occlusion was suspected. All patients were followed up from stent insertion until death or the end of the present study: 69 patients died from malignant diseases after a median follow-up of 6.1 months (ranged 0.5–32.4) and the other five patients have been followed up for a median of 11.4 months (ranged 6.4–12.3). Written informed consent was obtained from all patients in accordance with the Helsinki declaration.

Technique. Prophylactic treatment with broad-spectrum antibiotics was initiated for all patients. SEMS were placed endoscopically under fluoroscopic guidance and conscious sedation. After biliary cannulation and the obtainment of a cholangiogram, a 0.035-inch-diameter guidewire was passed through the stricture and inserted into the intrahepatic bile duct. Subsequently, the SEMS was inserted over the guidewire. Endoscopic sphincterotomy (EST) with middle incision was performed before SEMS placement, unless tumor invasion to the papilla of Vater, a bleeding tendency, or pancreaticobiliary maljunction was observed. The location and length of the stricture were evaluated by the cholangiogram. The appropriate SEMS length was selected; all the SEMSs were partially or fully covered type and measured 10 mm in diameter. The following three types of covered SEMS were used in this study: the Wallstent (Microvasive Endoscopy, Boston Scientific Corporation, Natick, MA, USA), the ComVi stent (Taewoong Medical, Seoul, Korea), and the WallFlex stent (Microvasive). We categorized these three SEMS by axial force (AF) and radial force (RF) according to a previous report.[8] Wallstent and WallFlex stents are categorized as high AF stents, whereas the ComVi stent is a low AF stent. On the other hand, the ComVi and WallFlex stents are categorized as high RF stents, and the Wallstent is a low RF stent. Prophylactic placement of the pancreatic duct stent was not performed in any of the cases.

Definition of complications. Pancreatitis was defined by using standard criteria:[9] new or worsening abdominal pain post-procedure in conjunction with an elevation in serum amylase or lipase levels greater than three times the upper limit of normal, with or without radiographic evidence of acute pancreatitis. The severity grading was as follows: mild, requiring prolongation of planned admission for 3 days or less; moderate, requiring 4–10 days of hospitalization; and severe, requiring more than 10 days of hospitalization, intensive care, or surgical intervention.

Cholecystitis was defined as follows: right upper quadrant tenderness (Murphy's sign) and/or fever after SEMS placement that was associated with radiologic evidence of cholecystitis on ultrasound or computed tomography (CT) imaging findings, such as swollen gallbladder, wall thickening, and pericholecystic effusions.

Methods

We evaluated the frequency of pancreatitis and cholecystitis. Pancreatitis was evaluated in all 74 patients, and cholecystitis was evaluated in the 66 patients who had not undergone cholecystectomy. Furthermore, we evaluated various parameters to clarify the predictive factors of pancreatitis and cholecystitis. The following 10 variables were evaluated in pancreatitis by univariate analysis: [1] sex, [2] age, [3] primary disease, [4] Covered type (partially or fully), [5] SEMS with high AF, [6] SEMS with high RF, [7] EST before SEMS, [8] previous biliary stent, [9] contrast injection into the pancreatic duct (pancreatogram), and [10] the position of the distal stent edge. The following 11 variables were evaluated in cholecystitis by univariate analysis: [1] sex, [2] age, [3] regions of stricture, [4] SEMS with high AF, [5] SEMS with high RF, [6] previous biliary stent, [7] gallbladder stone, [8] contrast injection into the gallbladder (GB injection), [9] involvement to the OCD, [10] position of distal stent edge, and [11] cystic duct occlusion by SEMS.

In this study, we evaluated tumor involvement to the OCD by endoscopic retrograde cholangiography (ERC) and/or magnetic resonance cholangiopancreatography (MRCP). We defined tumor involvement to the OCD when the cystic duct was derived from the common bile duct stricture caused by tumor. (Fig. 1)

Statistical analysis. Comparison of continuous variables and categorical variables were carried out using the Mann–Whitney *U*-test and the Fisher's exact test, respectively. The χ^2 test or the Fisher's exact test was used for univariate analysis. We included variables with $P < 0.2$ in a multivariate regression analysis. An odds ratio (OR) was used with 95% confidence intervals (CI). Statistical tests were two-sided and significance was defined as $P < 0.05$. All statistical analyses were performed using the JMP 8.0.2 software package (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. A total of 74 consecutive patients with distal MBO treated initially by covered SEMS placement were enrolled in this study. Subjects included 41 men (55.4%) and 33 women (44.6%) with a median age of 75.5 years (range 46–94). Cholecystectomy was performed in eight patients before SEMS placement. The primary diseases of MBO were pancreatic cancer in 56 patients (76%), cholangiocarcinoma in 10 (14%), gallbladder

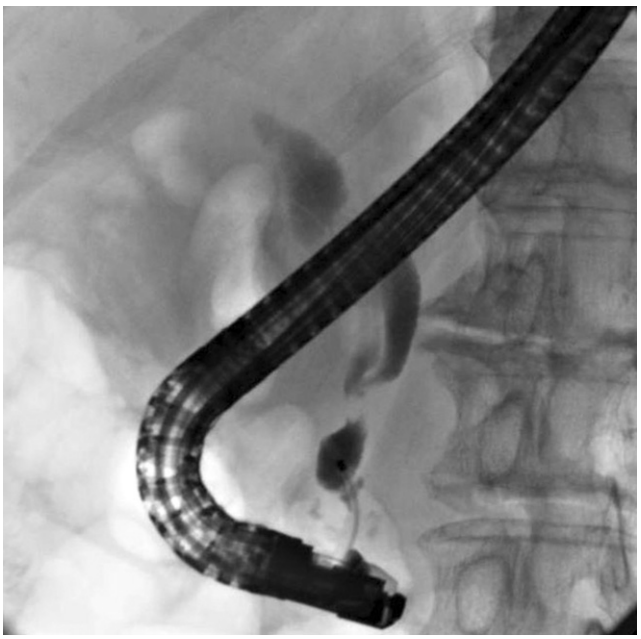

Figure 1 Endoscopic retrograde cholangiography (ERC) showed tumor involvement to the orifice of the cystic duct.

cancer in four (5%), and lymph node metastasis in four (5%). Biliary strictures were located in the lower and middle regions in 54 and 20 patients, respectively. The partially covered SEMSs were used in 31 patients and fully in 43, respectively. The covered SEMSs were used in the following proportions: the Wallstent in 20 patients (27%), the ComVi stent in 21 (28%), and the WallFlex stent in 33 (45%). EST was performed before SEMS placement in 53 patients (72%), and previous biliary stents were inserted in 48 patients (65%). Histological evidence of malignancy was confirmed in 46 patients (62%). Chemotherapy was administrated after SEMS placement in 39 patients (53%).

Pancreatitis. Pancreatitis after SEMS placement occurred in 8 of 74 patients (10.8%). The onset of pancreatitis was within 24 h in all cases. All cases of pancreatitis were mild according to the consensus criteria.[9] Conservative therapy without stent removal resulted in improvement in all of these patients. The median fasting period of these patients was 7 days (range 3–8) for the treatment of pancreatitis. The median of the maximum amylase and C-reactive protein levels after SEMS placement were 1711 U/mL (range 403–3248) and 6.8 mg/dL (range 1.6–32.0), respectively.

Table 1 shows the univariate analysis of risk factors for pancreatitis. Univariate analysis revealed that non-pancreatic cancer and contrast injection into the pancreatic duct were significant predictive factors for pancreatitis. The frequency of pancreatitis was significantly higher in patients with non-pancreatic cancer than in those with pancreatic cancer (27.8% *vs* 5.4%; $P = 0.018$). The frequency of pancreatitis was significantly higher in patients with contrast injection into the pancreatic duct than in those without (25.0% *vs* 5.6%; $P = 0.030$). The other seven variables were not significantly different between the pancreatitis group and the non-pancreatitis group.

Table 1 Univariate analysis of risk factors for pancreatitis

Variables	Pancreatitis	Non-pancreatitis	*P*-value
No. patients	8	66	
Sex (male : female)	5:3	36:30	0.725
Age (years), median (range)	78 (68–84)	75 (46–94)	0.663
Age (> 60: < 60)	8:0	57:9	0.584
PCa : non-PCa*	3:5	53:13	0.018*
Partially : Fully	5:3	26:40	0.267
High AF : Low AF	7:1	46:20	0.427
High RF : Low RF	5:3	49:17	0.674
EST (+ : –)	7:1	47:19	0.435
Previous biliary stent (+ : –)	4:4	44:22	0.440
Pancreatogram (+ : –)*	5:3	15:51	0.030*
Position of distal stent edge (Above the papilla : Across the papilla)	0:8	7:59	0.433

*$P < 0.05$.

AF, axial force; EST, endoscopic sphincterotomy; PCa, pancreatic cancer; RF, radial force.

Table 2 Multivariate analysis of risk factors for pancreatitis

Variables	OR	95%CI	*P*-value
Non-PCa*	3.43	1.44–10.05	0.010*
Pancreatogram*	3.17	1.32–9.29	0.015*

*$P < 0.05$.

CI, confidence interval; OR, odds ratio; Pca, pancreatic cancer.

In the multivariate logistic regression analysis, non-pancreatic cancer (OR, 3.43; 95% CI, 1.44–10.05; $P = 0.010$) and contrast injection into the pancreatic duct (OR, 3.17; 95% CI, 1.32–9.29; $P = 0.015$) were significant independent predictive risk factors for pancreatitis after SEMS placement (Table 2).

Cholecystitis. Cholecystitis after SEMS placement occurred in 4 of 66 patients (6.1%). The median time to onset of cholecystitis was 9 days (range 4–20) after stent placement. Cholecystitis was improved by conservative therapy with intravenous antibiotics in two of four patients, but the remaining two patients required percutaneous transhepatic gallbladder drainage (PTGBD). Surgical resection was not performed for any of these patients.

Table 3 shows the univariate analysis of risk factors for cholecystitis. Univariate analysis revealed that tumor involvement to the OCD was a significant predictive factor for cholecystitis. The frequency of cholecystitis was significantly higher in patients with tumor involvement to the OCD than in those without (37.5% *vs* 1.7%; $P = 0.005$). The other eight variables were not significantly different between the cholecystitis group and the non-cholecystitis group. In the multivariate logistic regression analysis, tumor involvement to the OCD was a significant independent predictive factor for cholecystitis (OR, 5.85; 95% CI, 1.91–27.74; $P = 0.005$). (Table 4)

Discussion

We clarified the predictive factors for pancreatitis and cholecystitis in patients with distal MBO after the placement of a covered

Table 3 Univariate analysis of risk factors for cholecystitis

Variables	Cholecystitis	Non-cholecystitis	*P*-value
No. patients	4	62	
Sex (male : female)	1:3	34:28	0.335
Age (years), median (range)	79 (60–84)	75 (46–89)	0.757
Age (> 70: < 70)	3:1	20:42	0.118
Regions of stricture (Bm : Bi)	1:3	15:47	1
High AF : Low AF	4:0	43:19	0.288
High RF : Low RF	3:1	44:18	1
Previous biliary stent (+ : –)	1:3	43:19	0.104
GB stone(+ : –)	1:3	13:49	1
GB injection (+ : –)	0:4	24:38	0.288
Involvement to OCD (+ : –)**	3:1	5:57	0.005**
Position of distal stent edge (Above the papilla : Across the papilla)	0:4	7:55	0.632
Cystic duct occlusion by SEMS (+ : –)	4:0	56:6	1

** $P < 0.01$.

AF, axial force; EST, endoscopic sphincterotomy; GB, gallbladder; OCD, orifice of the cystic duct; Pca, pancreatic cancer; RF, radial force; SEMS, self-expandable metal stent.

Table 4 Multivariate analysis of risk factors for cholecystitis

Variables	OR	95%CI	*P*-value
Previous biliary stent	1.54	0.40–7.70	0.528
Involvement to OCD*	4.91	1.47–24.86	0.017*

* $P < 0.05$.

CI, confidence interval; OCD, orifice of the cystic duct; OR, odds ratio.

SEMS. Non-pancreatic cancer and contrast injection into the pancreatic duct were significant independent predictive factors for pancreatitis. On the other hand, tumor involvement to the OCD was a significant independent predictive factor for cholecystitis.

In general, endoscopic drainage with SEMS is accepted as the first-line palliative therapy for the treatment of unresectable MBO because of its low invasiveness and long stent patency. The patency of the SEMS is superior to that of the plastic stent. However, SEMS placement is associated with several complications and management of these complications is very important in order to protect the quality of life for these patients. Pancreatitis and cholecystitis are two major complications in distal MBO. In the present study, the rates of pancreatitis and cholecystitis were 10.8% (8/74) and 6.1% (4/66), respectively. The rate of pancreatitis after SEMS placement reportedly ranges from 0.8% to 8.7% and the rate of cholecystitis ranges from 5.8% to 11.5%.[6,10–15] In our study, the incidence of pancreatitis was higher than in previous reports whereas that of cholecystitis was similar to previous reports.

Several predictive factors such as young age, female gender, contrast injection into the pancreatic duct, sphincter of Oddi, and a history of post-ERCP pancreatitis have been reported for post-ERCP pancreatitis. However, only a few reports have described predictive factors for pancreatitis after SEMS placement in distal MBO. Non-pancreatic cancer and SEMS with high AF were reported as predictive factors.[3] In the present study, multivariate analysis revealed that non-pancreatic cancer and contrast injection into the pancreatic duct were significant independent predictive factors for pancreatitis.

Non-pancreatic cancer was a predictive factor for pancreatitis in both the present and previous studies. Isayama and Nakai *et al*. reported that the incidence of pancreatitis in patients with main pancreatic duct (MPD) tumor involvement was low.[2,16] MPD was involved in most cases with pancreatic cancer and usually obstructed with the tumor and distal pancreas is atrophic. Therefore, exocrine function is usually decreased in patients with pancreatic cancer, whereas exocrine function is usually preserved in patients with non-pancreatic cancer. This observation might explain the finding that non-pancreatic cancer is a predictive factor for pancreatitis.

Contrast injection into the pancreatic duct was a significant independent predictive factor for pancreatitis in the present study. Although contrast injection into the pancreatic duct has been reported as one of the predictive factors for post-ERCP pancreatitis, it has not been reported as a predictive factor for pancreatitis after SEMS placement. We believe that it is important to avoid unnecessary pancreatograms when performing SEMS placements for distal MBO. Prophylactic placement of pancreatic duct stent might decrease the risk of pancreatitis after SEMS placement especially for patients with non-pancreatic cancer because its efficacy at preventing post-ERCP pancreatitis in high-risk patients has been established in several randomized controlled trials.[17–19]

Tumor involvement to the OCD and the presence of a gallbladder stone were reported as predictive factors for cholecystitis after SEMS placement.[6,7] In the present study, tumor involvement to the OCD was a significant independent predictive factor for cholecystitis, whereas the presence of a gallbladder stone was not. Isayama *et al*., who evaluated tumor involvement to the OCD by using biliary intraductal ultrasonography (IDUS), reported that tumor involvement to the OCD was the only independent predictor for cholecystitis after SEMS placement according to their multivariate analysis.[7] Nakai *et al*. reported that IDUS was superior to ERCP in terms of assessing tumor involvement.[20] Although we agree that IDUS is superior to ERC or MRCP for exact evaluation of tumor involvement to the OCD, we evaluated tumor involvement to the OCD by MRCP and/or ERC without using biliary IDUS in the present study. Some facilities do not have the IDUS device;

further, we are also not always able to use IDUS during ERCP for practical purposes. Therefore, the results of our multivariate analysis without using IDUS in diagnosing tumor involvement to the OCD may be meaningful.

In the previous report by Isayama *et al*., SEMSs were categorized into several groups according to RF and AF.[8] Kawakubo *et al*. reported that SEMSs with high AF were strongly associated with a high incidence of pancreatitis following transpapillary SEMS placement in patients with distal MBO.[3] They explained that the high risk of pancreatitis was due to medial deflection of the stent and compression of the orifice of the pancreatic duct. However, high AF did not contribute to pancreatitis after covered SEMS placement in our present analysis.

Treatment of acute cholecystitis after SEMS placement may involve conservative therapy with antibiotics, PTGBD, or surgical resection, depending on the severity of the disease. Because many patients have inoperable conditions, PTGBD is an effective treatment for cholecystitis because of its less-invasive drainage techniques. However, PTGBD is associated with pain derived from puncture and decreases the activity of daily living of the patient because of the necessity of managing the drainage tube. The feasibility, efficacy, and morbidity of the transpapillary gallbladder stent (GBS) in the prevention of cholecystitis in patients who underwent covered SEMS placement for distal MBO have been described.[21] Although transpapillary GBS is a promising technique that does not require puncture of the gallbladder or maintenance of the drainage tube, placement of a drainage tube in the gallbladder via the cystic duct is technically difficult and may even be impossible in some cases. Presently, endosonography-guided gallbladder drainage (ESGBD) is performed in some cases.[22] We consider that cholecystitis after SEMS placement is a good indication for ESGBD if this technique is well established. Therefore, it is important to predict the risk of cholecystitis before performing SEMS placement for distal MBO.

This study has several limitations. These include the retrospective and uncontrolled study design, the relatively low number of available patients, and the fact that different types of stents were used for each stent deployment. Therefore, a prospective, randomized controlled trial with the same kind of stents and a larger number of patients must be conducted.

In conclusion, non-pancreatic cancer and contrast injection into the pancreatic duct were predictive factors for pancreatitis, and tumor involvement to the OCD was a predictive factor for cholecystitis after endoscopic covered SEMS placement for distal MBO in the multivariate analysis.

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