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ENDOSCOPY

Features of post-endoscopic submucosal dissection electrocoagulation syndrome for early gastric neoplasm

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Abstract

Background and Aim: Post-endoscopic submucosal dissection electrocoagulation syndrome (PECS) has become a common adverse event after colorectal endoscopic submucosal dissection (ESD) and esophageal ESD. However, little is known about PECS after gastric ESD. Therefore, this study aimed to investigate the clinical features of PECS after gastric ESD.
Methods: Patients who underwent ESD for gastric cancer or adenoma between January 2016 and December 2017 were retrospectively investigated. PECS was clinically diagnosed based on the presence of upper abdominal pain and localized abdominal tenderness with a temperature of >37.5°C, without perforation. We analyzed the clinical features of PECS.
Results: A total of 637 ESD cases were enrolled; PECS occurred in 32 patients (5.0%), all of whom were diagnosed on postoperative Day 1. Among PECS cases, unplanned prolongation of hospitalization or fasting period was observed in 15 patients (47%). As a result, the median durations of hospitalization and fasting period were significantly longer in PECS cases ($P = 0.008$ and $P < 0.001$, respectively); however, the mean differences were less than a day. Additionally, all PECS cases recovered with conservative treatment.
Conclusions: PECS is considered a common adverse event after gastric ESD. More than half of patients with PECS could start diets and be discharged as well as those without PECS.

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Introduction

Endoscopic submucosal dissection (ESD) is now widely performed as an advanced minimally invasive treatment for early gastric neoplasms.[1–5] However, ESD requires a high level of technical expertise and is associated with a risk of complications,[6] of which bleeding and perforation are considered major complications during gastric ESD.[5–7] In addition, in clinical practice, we sometimes encounter patients who complain of fever and abdominal pain after ESD.

Post-endoscopic submucosal dissection electrocoagulation syndrome (PECS) is considered a thermal transmural injury caused by electrocoagulation after ESD and is characterized by fever and localized pain without perforation. PECS has become a common adverse event after colorectal ESD[8–17] and esophageal ESD[18–20]; the incidence of PECS was reported to be 4.8%–40.2%[8–17] in colorectal ESD and 11%–54.8%[18–20] in esophageal ESD. However, only one previous study reported the clinical features of PECS after gastric ESD[21] and did not describe the clinical course of PECS in detail, including the timing of PECS occurrence

and the post-discharge course of PECS. Therefore, it remains unclear how PECS should be clinically managed after gastric ESD. Thus, this study investigated the clinical features of PECS and the management of patients with PECS after ESD for early gastric neoplasms.

Methods

Patients. This was a retrospective observational study. From January 2016 to December 2017, consecutive patients with early gastric cancer or adenoma who underwent gastric ESD at a single tertiary cancer center were enrolled. The exclusion criteria were as follows: (i) patients who underwent ESD for synchronous gastric neoplasms or multiple tumors on the same day; (ii) perforation; (iii) patients receiving antibiotic treatment due to an infectious disease before or after ESD; and (iv) a history of gastrectomy or esophagectomy (gastric tube case). Although only ESD cases with a single gastric neoplasm during a single hospital stay were included in the present study, patients who underwent ESD for metachronous gastric neoplasms after ESD on another day more than 3 months apart during the study period were also included.

This study was approved by the Institutional Review Board of the Shizuoka Cancer Center (Institutional No. J2020-98-2020-1-3) on October 13, 2020. Written informed consent was obtained from all patients before treatment.

Endoscopic submucosal dissection procedure and management after endoscopic submucosal dissection. The ESD procedure has been described previously.[22,23] Briefly, ESD was performed using a standard single-accessory channel endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with a transparent disposable cap (elastic touch; Top, Tokyo, Japan). A mixture of 0.4% sodium hyaluronate acid (Muco Up; Boston Scientific Japan, Tokyo, Japan) and saline solution, combined with indigo carmine, was injected into the submucosal layer. Mucosal incision and submucosal dissection were performed using an IT knife2 (KD-611L; Olympus) in the endo-cut Q mode (effect 2, duration 3, and interval 2, VIO300D; ERBE, Germany) and swift coagulation mode (effect 5, 100 W), respectively. During ESD, hemostasis was achieved using either the knife itself with the swift coagulation mode (effect 5, 100 W) or hemostatic forceps using the soft coagulation mode (effect 6, 100 W). If perforation was recognized during ESD, intravenous antibiotic therapy was immediately started, and perforation closure was performed using clips. After the completion of ESD, post-ESD coagulation (PEC) is usually performed regardless of the presence of bleeding.[24] All visibly exposed vessels on the ESD ulcer were coagulated using hemostatic forceps in the soft coagulation mode.

All patients routinely underwent blood tests, chest and abdominal X-rays, and a second-look endoscopy on postoperative day (POD) 1. After that, the patients without any complications started drinking water on POD 1, began eating a soft diet on POD 2, and were discharged on POD 4. The duration of hospitalization was sometimes extended depending on their symptoms after starting the diet. The patients were followed up in the outpatient setting at 2–4 weeks after discharge. Proton pump inhibitors were started on POD 0 and prescribed for up to 2 months after ESD.

Basically, patients with PECS were observed with no therapeutic interventions. If fever and symptoms of patients with PECS tended to improve, patients with PECS, as well as those without PECS, were started on a diet and subsequently discharged. However, if the fever and abdominal pain did not improve, blood cultures, computed tomography (CT) imaging, antibiotics, delaying the start of the soft diet, and/or extension of the hospitalization period were performed. In addition, if mild abdominal pain remained at discharge, we prescribed acetaminophen for use as needed.

Definition and data collection. The PECS was clinically diagnosed based on the presence of upper abdominal pain and localized abdominal tenderness with a temperature of $>37.5°C$, without perforation. Perforation was defined as a gross defect, with extraluminal organs, fatty tissues, or space visible through the lesion[21] during ESD or second-look endoscopy, or free air on X-ray or CT images after ESD. The endoscopic images of ESD ulcers were usually taken before and after PEC. Further, the PEC time was calculated by subtracting the time taken before the PEC from that taken after the PEC. The ESD procedure time was defined as the time from the start of the submucosal injection to the completion of resection. Delayed bleeding was defined as clinical evidence of bleeding (hematemesis or melena) after ESD, requiring blood transfusion or endoscopic or surgical intervention.

Clinicopathological information was retrospectively collected from the institutional electronic records and analyzed. We analyzed the clinical features of PECS and assessed the risk factors for PECS.

Statistical analysis. All continuous variables are reported as the median and interquartile range (IQR). All categorical variables are reported as n (%). As for the hospitalization and fasting periods, they are presented as not only the median and IQR but also the mean and standard deviation (SD). Univariate and multivariate analyses were performed to identify the risk factors related to PECS: age, sex, tumor location, endoscopists, tumor size, PEC time, ESD procedure time, resected specimen size, and pathological invasion depth. In the univariate analysis, we used the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Regarding the PEC time, ESD procedure time, and the resected specimen size, the cut-off values were determined on the basis of a receiver operating characteristic (ROC) curve. If the area under the curve (AUC) was less than 0.7, the cut-off value was determined as the closest round number to the calculated value. Factors with $P < 0.1$ in the univariate analyses were included in a multivariate logistic regression analysis (backward, stepwise). If multicollinearity between significant factors identified in the multivariate analysis was suspected, Spearman's rank correlation coefficient was calculated to evaluate the correlation between these factors. We calculated the odds ratios (OR) and 95% confidence intervals (95% CIs) to assess the strength of the influence of each individual variable. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using EZR software version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Baseline characteristics and clinical features of post-endoscopic submucosal dissection electrocoagulation syndrome. Between January 2016 and December 2017, a total of 909 patients (1207 lesions) underwent ESD at our institution. Finally, 637 ESD cases (615 patients, 637 lesions) were enrolled in this study. In the study period, 19 patients underwent ESD for metachronous gastric neoplasms after ESD during another hospitalization period. The patient flow diagram is shown in Figure 1.

The baseline characteristics are summarized in Table 1. Of the enrolled cases, PECS occurred in 32 cases (5.0%) after gastric ESD. PECS was diagnosed on POD 1 in all PECS cases. Compared with no PECS cases, the proportion of female patients and resected ESD specimen size were significantly larger in PECS cases (56% *vs* 26%, $P < 0.001$; 45 mm *vs* 40 mm, $P = 0.002$). In addition, the PEC time was significantly longer in PECS cases (7 min *vs* 5 min, $P < 0.001$), while there was no significant difference in the ESD procedure time (36 min *vs* 33 min, $P = 0.26$) between PECS and no PECS cases.

Table 1 Baseline characteristics of patients undergoing gastric endoscopic submucosal dissection

	PECS 32 cases	No PECS 605 cases
Age, median (IQR), years	74 (65–78)	72 (66–78)
Sex, male (%)	14 (44)	449 (74)
Medication		
NSAIDs	0 (0)	17 (3)
Aspirin	2 (6)	72 (12)
Warfarin	1 (3)	14 (2)
Direct oral anti-coagulants	1 (3)	14 (2)
Tumor location (%)		
Upper third	7 (22)	107 (18)
Middle third	15 (47)	242 (40)
Lower third	10 (31)	256 (42)
Main macroscopic type (%)		
Depressed	22 (69)	373 (62)
Flat elevated	9 (28)	214 (35)
Protruded	1 (3)	18 (3)
Operator (%)		
Expert	17 (53)	267 (44)
Trainee	15 (47)	338 (56)
Post-ESD coagulation time, median (IQR), min	7 (5–9)	5 (3–6)
Procedure time, median (IQR), min	36 (24–68)	33 (20–57)
Resected specimen size, median (IQR), mm	45 (38–65)	40 (32–48)
Closure of ESD ulcer (%)	1 (3)	47 (8)
Pathological invasion depth (%)		
Adenoma	1 (3)	26 (4)
Mucosal invasion	28 (88)	504 (83)
Submucosal invasion	3 (9)	75 (12)

ESD, endoscopic submucosal dissection; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; PECS, post-endoscopic submucosal dissection electrocoagulation syndrome.

Clinical course after gastric endoscopic submucosal dissection. The clinical course of gastric ESD is described in Table 2. Regarding blood tests, the C-reactive protein level on POD 1 was significantly higher in PECS cases (0.62 mg/dL *vs* 0.47 mg/dL, $P = 0.049$), while white blood cell counts on POD 1 were not significantly different (9545/μL *vs* 9340/μL, $P = 0.56$). Among PECS cases, unplanned prolongation of hospitalization or fasting period was observed in 15 patients (47%). As a result, the median durations of the hospitalization and fasting period were significantly longer in PECS cases ($P = 0.008$ and $P < 0.001$, respectively); however, these mean differences were less than a day. Furthermore, no significant difference in the incidence of delayed bleeding was observed between the two groups (9.4% for PECS cases *vs* 6.4% for no PECS cases, $P = 0.46$).

Of the 32 patients with PECS, five received antibiotic therapy, and seven underwent blood culture examinations; bacteremia was not observed in any cases. In addition, all PECS cases recovered with conservative treatment. All PECS cases were followed up at several weeks (median, 19 days; IQR, 16–21 days) after discharge. There were no cases of re-exacerbation of abdominal pain or readmission due to PECS. Of the 32 enrolled patients with PECS, two had mild abdominal pain at discharge and were prescribed acetaminophen for use, as needed. The symptoms of these two patients improved at 1 and 5 days after discharge, respectively.

Assessment of risk factors for post-endoscopic submucosal dissection electrocoagulation syndrome. The risk factors for PECS are shown in Table 3. Based on the ROC curve, the cut-off values for the PEC time, ESD

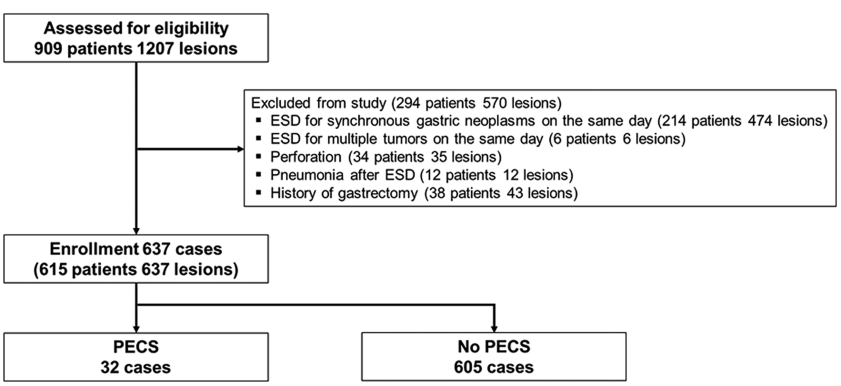

Figure 1 Patient flow diagram. PECS, post-endoscopic submucosal dissection electrocoagulation syndrome; ESD, endoscopic submucosal dissection.

Table 2 Clinical course after gastric endoscopic submucosal dissection

	PECS 32 cases	No PECS 605 cases	*P* value
Hospitalization, median (IQR), days	5 (5–7)	5 (4–5)	0.008
Hospitalization, mean ±SD, days	5.8 ± 1.5	5.2 ± 1.7	
Fasting period, median (IQR), days	2 (2–3)	2 (2–2)	<0.001
Fasting period, mean± SD, days	2.3 ± 0.5	2.0 ± 0.2	
Duration of fever >37.5°C, median (IQR), hours	11 (4–18)	0 (0–0)	<0.001
White blood cell count on POD 1, median (IQR), /μL	9545 (7998–11 550)	9340 (7742–10 880)	0.56
C-reactive protein level on POD 1, median (IQR), mg/dL	0.62 (0.43–1.24)	0.47 (0.24–0.85)	0.049
Delayed bleeding (%)	3 (9.4)	39 (6.4)	0.46

IQR, interquartile range; PECS, post-endoscopic submucosal dissection electrocoagulation syndrome; POD, postoperative day; SD, standard deviation.

procedure time, and resected specimen size were 7, 32, and 56 mm with sensitivities of 59.4%, 65.6%, and 40.6%, specificities of 75.9%, 47.6%, and 87.8%, and AUCs of 0.717, 0.559, and 0.665, respectively. Because the AUCs for the ESD procedure time and resected specimen size were less than 0.7, and because 32 and 56 were not meaningful numbers, the cut-off values were determined to be 30 min for the ESD procedure time and 60 mm for the resected specimen size. In the multivariate analysis, female sex (OR 3.6, 95% CI 1.7–7.7, $P < 0.001$), PEC time ≥7 min (OR 3.8, 95% CI 1.8–8.0, $P < 0.001$), and resected specimen size ≥60 mm (OR 3.4; 95% CI 1.5–7.9; $P = 0.005$) were significantly associated with PECS. We also confirmed a quite weak correlation between PEC time and resected specimen size (correlation coefficient 0.142, Fig. S1), suggesting that the possibility of multicollinearity was low.

Discussion

This study retrospectively investigated the clinical features and risk factors of PECS for early gastric neoplasms. In this study, PECS occurred in 5.0% of the cases after gastric ESD. All PECS cases recovered with conservative treatment, and more than half of patients with PECS could start diets and be discharged as well as those without PECS.

Several studies have reported the clinical features of PECS in colorectal ESD[8–17] and esophageal ESD,[18–20] while only one study evaluated those of PECS in gastric ESD.[21] Lee *et al.*[21] reported that coagulation syndrome occurred with an incidence of

Table 3 Assessment of risk factors for post-endoscopic submucosal dissection electrocoagulation syndrome

	PECS	No PECS	Univariate analysis		Multivariate analysis	
	32 cases	605 cases	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years (%)						
<65	8 (25)	102 (17)	Reference			
≥65	24 (75)	503 (83)	0.61 (0.26–1.6)	0.23		
Sex (%)						
Male	14 (44)	449 (74)	Reference			
Female	18 (56)	156 (26)	3.7 (1.7–8.2)	<0.001	3.6 (1.7–7.7)	<0.001
Tumor location (%)						
Upper third	7 (22)	107 (18)	1.7 (0.53–5.0)	0.29		
Middle third	15 (47)	242 (40)	1.6 (0.65–4.0)	0.31		
Lower third	10 (31)	256 (42)	Reference			
Endoscopists (%)						
Expert	17 (53)	267 (44)	1.4 (0.66–3.1)	0.36		
Trainee	15 (47)	338 (56)	Reference			
Post-ESD coagulation time, min (%)						
<7	13 (41)	459 (76)	Reference			
≥7	19 (59)	146 (24)	4.6 (2.1–10.4)	<0.001	3.8 (1.8–8.0)	<0.001
Procedure time, min (%)						
<30	11 (34)	262 (43)	Reference			
≥30	21 (66)	343 (57)	1.5 (0.66–3.4)	0.36		
Resected specimen size, mm (%)						
<60	22 (69)	546 (90)	Reference			
≥60	10 (31)	59 (10)	4.2 (1.7–9.8)	0.001	3.4 (1.5–7.9)	0.005
Pathological invasion depth (%)						
Mucosal invasion or adenoma	29 (91)	530 (88)	Reference			
Submucosal invasion	3 (9)	75 (12)	0.73 (0.14–2.4)	0.79		
Closure of ESD ulcer						
Yes	1 (3)	47 (8)	0.38 (0.009–2.4)	0.50		
No	31 (97)	558 (92)	Reference			

95% CI, 95% confidence interval; ESD, endoscopic submucosal dissection; OR, odds ratio; PECS, post-endoscopic submucosal dissection electrocoagulation syndrome.

7.1% after gastric ESD. In our study, PECS after gastric ESD occurred in 5.0% of the patients. Based on these results, PECS after gastric ESD was considered a relatively common adverse event.

In the multivariate analysis, female sex, PEC time ≥7 min, and a resected specimen size ≥60 mm were significantly associated with PECS after gastric ESD. Female sex has been reported as an independent risk factor for PECS in colorectal ESD.[10,11,13] The descending pain sense pathway is different between men and women, and women have a lower tolerance and threshold for pain stimulation than men.[11,25] When considering the above studies, it makes sense that PECS is more likely to occur in women than in men. Regarding resected specimen size, previous studies of colorectal and esophageal areas also identified it as an independent risk factor for PECS.[8,10,18,19] A previous study[21] on PECS after gastric ESD reported that the middle third of the stomach, a tumor size ≥1.5 cm, and an ESD procedure time ≥45 min were significant risk factors for PECS after gastric ESD. Although a large size was identified as an independent risk factor for PECS in both the previous study and our study, other results in the previous study were different from our results. Contrary to a previous report,[21] PEC time (not ESD procedure time) was significantly associated with PECS. Although the IT knife was mainly used for ESD in both studies, the procedure time was shorter, and the PEC time was longer in our study than in the previous study (33 min *vs* 44.8 min; 5 min *vs* 3.7 min). Therefore, it is possible that the main thermal injury to the muscle layer occurred during the PEC rather than during the ESD procedure, which might have affected our results.

Regarding the clinical features of PECS after gastric ESD, the median duration of the hospitalization and fasting periods was significantly longer in PECS cases, but these mean differences were less than a day. In addition, no cases of bacteremia were observed, and all patients with PECS recovered with conservative treatment. A previous study[21] showed that the duration of hospital stay was significantly longer (7.3 days *vs* 4.4 days) and all patients with PECS recovered with conservative treatment. The number of days of extended hospital stay was higher in the previous study than in our study. However, the previous study[21] did not state the criteria for diet initiation and discharge among patients with PECS. In the previous study, the mean hospital stay was 4.4 days in the non-PECS group and 7.3 days in the PECS group, which was longer than that in our study, suggesting that patients with PECS were more carefully monitored and started diets after the disappearance of symptoms despite no explicit criteria for them. In our hospital, when symptoms tend to improve, diets for patients are started as soon as possible because early feeding has been reported by previous studies to be associated with a higher quality of life and does not affect the complication rates[26,27]; if symptom exacerbation does not occur, they are discharged. In fact, in our study, more than half of patients with PECS could start diets and be discharged as well as those without PECS, and there were no cases of readmission due to PECS. Therefore, we consider the aforementioned management to be appropriate for patients with PECS. Among the independent risk factors for PECS in our study, PEC time could be modifiable. However, PECS contributes to a slight prolongation of hospitalization or fasting period, and the difference in median PEC time between PECS cases and no PECS cases was only 2 min. Therefore, we may not need to be immensely concerned about the PEC time, considering the benefit of reducing the risk of delayed bleeding after gastric ESD.[24]

This study has several limitations. First, this was a retrospective study performed at a single medical center, resulting in a potential selection bias. Further multicenter studies are required to validate our results. Second, not all patients with PECS received blood cultures, and it was difficult to ascertain whether there was really no bacteremia. However, in a previous study,[21] all patients with PECS received blood cultures, and there were no cases of bacteremia. Furthermore, all patients with PECS conservatively improved not only in the previous study[21] but also in our study. Additionally, two prospective studies[28,29] reported that all blood cultures obtained at several hours after gastric ESD were negative in non-perforation cases, although fever often occurred. The results are similar to those in colorectal ESD[30] and esophageal ESD.[31] Therefore, PECS is unlikely to be associated with bacteremia but is considered a thermal transmural injury caused by electrocoagulation. Third, this study excluded patients who underwent ESD for a synchronous gastric neoplasm on the same day, which might be a risk factor for PECS after gastric ESD. If such patients were included, we could not interpret the effects of risk factors such as tumor location, pathological invasion depth, and resected specimen size on PECS. Hence, we included only ESD cases with a single gastric neoplasm during a single hospital stay, as in a previous study.[21] Fourth, CT was not performed in all PECS cases, and it was difficult to deny microperforation. However, in all ESD cases, radiography was performed on the day after ESD to confirm visible free air, and endoscopy was conducted not only during ESD but also on the day after ESD to observe the ulcer. Therefore, it is unlikely that microperforation cases account for the majority of PECS cases.

In conclusion, PECS is considered a common adverse event after gastric ESD. More than half of patients with PECS could start diets and be discharged as well as those without PECS.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlation between PEC time and resected specimen size. ESD, endoscopic submucosal dissection; PEC, post-ESD coagulation.