ORIGINAL ARTICLE

Retrospective Study

Risk factors of electrocoagulation syndrome after esophageal endoscopic submucosal dissection

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Abstract

AIM

To investigate post endoscopic submucosal dissection electrocoagulation syndrome (PEECS) of the esophagus.

METHODS

We analyzed 55 consecutive cases with esophageal endoscopic submucosal dissection for superficial esophageal squamous neoplasms at a tertiary referral hospital in South Korea. Esophageal PEECS was defined as "mild" meeting one of the following criteria without any obvious perforation: fever ($\geqslant 37.8\ ^{\circ}\text{C}$), leukocytosis (> 10800 cells/μL), or regional chest pain more than 5/10 points as rated on a numeric pain intensity scale. The grade of PEECS was determined as "severe" when meet two or more of above criteria.

RESULTS

We included 51 cases without obvious complications

in the analysis. The incidence of mild and severe esophageal PEECS was 47.1% and 17.6%, respectively. Risk factor analysis revealed that resected area, procedure time, and muscle layer exposure were significantly associated with PEECS. In multivariate analysis, a resected area larger than 6.0 cm^2 (OR = 4.995, 95%CI: 1.110-22.489, P = 0.036) and muscle layer exposure (OR = 5.661, 95%CI: 1.422-22.534, P = 0.014) were independent predictors of esophageal PEECS. All patients with PEECS had favorable outcomes with conservative management approaches, such as intravenous hydration or antibiotics.

CONCLUSION
Clinicians should consider the possibility of esophageal PEECS when the resected area exceeds 6.0 cm^2 or when the muscle layer exposure is noted.

Key words: Electrocoagulation; Endoscopic submucosal dissection; Esophageal neoplasm; Syndrome

Core tip: A number of patients experience fever, chest pain, and/or a systemic inflammatory response after esophageal endoscopic submucosal dissection, even in the absence of obvious perforation. Post endoscopic submucosal dissection electrocoagulation syndrome which is characterized by fever, leukocytosis, and chest pain has been found to be a relatively common condition after esophageal endoscopic submucosal dissection. It more frequently occurs when the resection area is wide (OR = 4.995) or when there is muscle layer damage (OR = 5.661), but it is restored without significant sequelae by conservative treatment.

INTRODUCTION

With the development of endoscopic imaging technology and the increase in early endoscopic surveillance, the incidence of superficial esophageal neoplasm (SEN) has increased substantially[1,2]. Endoscopic resection has been considered to be a feasible procedure for SEN because of its minimal invasiveness and the fact that it does not compromise organ function[3,4]. Endoscopic submucosal dissection (ESD) is an endoscopic resection method that enables high rates of en bloc resection regardless of tumor size and consequently reduces local recurrence[5,6]. However, esophageal ESD is a more difficult procedure to perform than gastric ESD. The

technical resectability of the lesion is affected by various applied techniques, the expertise of the endoscopist, and the location and/or features of the lesion[1,6].

Well-known complications of esophageal ESD include perforation (0%-6.9%), bleeding (0%-5.2%), and post-procedural stricture (0%-17.2%)[1,4,7-10]. However, post ESD electrocoagulation syndrome (PEECS) can be also a common complication of ESD[11,12]. PEECS is characterized by localized abdominal pain, rebound tenderness, fever, and signs of peritoneal irritation without frank perforation after gastric or colorectal ESD. Several previous studies analyzed PEECS after gastric or colonic ESD, but PEECS after esophageal ESD has not been studied yet[12,13]. Actually, some patients demonstrate clinical signs of PEECS after esophageal ESD associated with fever, chest pain and leukocytosis, despite the absence of perforation. However, the possibility of PEECS in the esophagus has received little attention. As far as we know, no studies have yet been conducted on PEECS in the esophagus, and we tried to investigate this new study. Therefore, we aimed to evaluate the incidence and risk factors of PEECS in the esophagus.

MATERIALS AND METHODS

Patients and tumors
We retrospectively analyzed prospectively collected database of patients who underwent esophageal ESD for superficial esophageal squamous neoplasms between March 2009 and December 2016 at Gangnam Severance Hospital, Seoul, South Korea. The analyzed demographic data and clinicopathologic features included patient age, sex, comorbidities, smoking and alcohol history, gross appearance of the tumor, location of the tumor, histological type, invasion depth, circumferential extension of the tumor, area of resection, degree of exposure of the muscularis propria, procedure time, systemic inflammatory response markers (*e.g.*, leukocyte count and body temperature), administration of antibiotics, and hospitalization period. The gross appearance of the tumor was categorized according to the Paris classification system[14]. Tumor histology was assigned according to the Japanese Classification of Esophageal Carcinoma scheme[15]. Tumor location was classified according to the guidelines of the American Joint Committee on Cancer[16]. The resected specimen was assumed to have an elliptical shape. Therefore, the resected area was calculated using the major and minor specimen axes, both of which were measured by a pathologist. The procedure time for ESD was defined as the time from circumferential marking to the retrieval of the resected specimens by an endoscope. Proper muscle layer exposure was defined as when the fine texture of the muscle fibers of muscularis propria was clearly exposed and visible endoscopically due to deep submucosal dissection (Figure 1). Patients who underwent multiple esophageal ESD were excluded in this study.
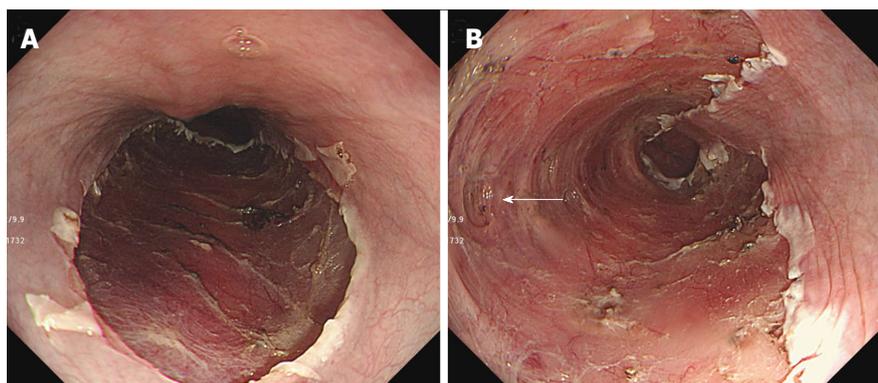
Figure 1 Proper muscle layer exposure during endoscopic submucosal dissection in esophagus. A: Absent; B: Present.
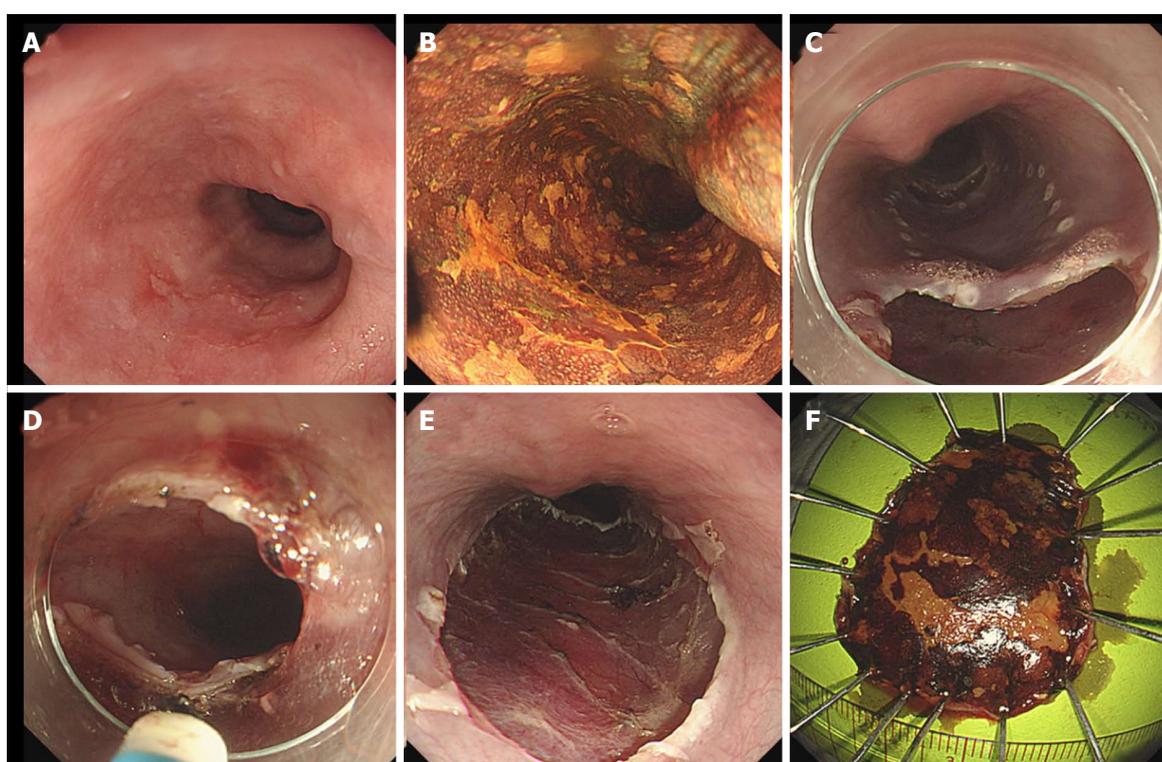
Figure 2 Endoscopic submucosal dissection of a superficial esophageal neoplasm. A and B: A flat erythematous lesion that is unstained with Lugol's solution; C and D: Endoscopic submucosal dissection is made with a dual-knife after local submucosal injection; E and F: The lesion is completely resected.

PEECS was defined as meeting following criteria: fever ($\geqslant 37.8$ ℃), leukocytosis (> 10800 counts/μL), or regional chest pain greater than 5/10 points as assessed on a numeric pain rating scale within 24 h after ESD[11,12]. Patients indicated the intensity of current, best, and worst pain levels on a scale of 0 (no pain) to 10 (worst pain imaginable)[17]. If one of the criteria was met, it was defined as mild PEECS and defined as severe PEECS if two or more criteria were met. Patients who had ESD complications such as overt perforation or bleeding were excluded from the analyses. Overt perforation was defined as radiographic evidence of free air, mediastinal emphysema, or subcutaneous emphysema after the procedure. Massive bleeding was defined as bleeding that led to the termination of the

procedure. Patients with other defined infections such as pneumonia were also excluded. The Institutional Review Board (IRB) of Gangnam Severance Hospital approved this study (3-2017-0163). We received a consent exemption from the IRB. Patients records and information was anonymized

ESD procedures
All ESD procedures were performed by two expert ESD endoscopists (Y.Y.H. and J.K.). Patients were moderately sedated with midazolam and propofol while ESD was performed. A video endoscope with a water-jet function (GIF-HQ290, GIF-Q260J; Olympus, Tokyo, Japan) was used. A disposable distal transparent cap (D-201-11804; Olympus) was mounted on the tip of

Table 1 Baseline patient and tumor characteristics *n* (%)

Characteristic	Value (*n* = 51)
Number of patients	51
Sex	
Male	46 (90.2)
Female	5 (9.8)
Age, mean ± SD, yr	63.6 ± 9.4
Comorbidity	
Hypertension	21 (41.2)
Diabetes mellitus	7 (13.7)
Chronic kidney disease	1 (2.0)
Smoker	42 (82.4)
Alcohol consumption	40 (78.4)
Gross appearance of tumor	
Polypoid	1 (2.0)
Elevated	8 (15.7)
Flat	40 (78.4)
Depressed	2 (3.9)
Location of tumor	
Upper third of esophagus	3 (5.9)
Middle third of esophagus	20 (39.2)
Lower third of esophagus	24 (47.1)
Esophagogastric junction	4 (7.8)
Circumferential extension, median (IQR), %	40 (30-60)
Pathology of tumor	
Dysplasia	14 (27.5)
Squamous cell carcinoma	37 (72.5)
Invasion depth of tumor	
Mucosa	38 (74.5)
Submucosa	13 (25.5)
Resected area, median (IQR), cm^2	4.5 (2.9-8.2)
Procedure time, median (IQR), min	40 (27-69)
Muscle layer exposure	
Absent	27 (52.9)
Present	24 (47.1)
En bloc resection	51 (100)
Antibiotics use	23 (45.1)
Post procedure BT, mean ± SD, ℃	36.6 ± 0.5
Post procedure WBC, median (IQR), counts/μL	10800 (9340-12600)
Post procedure pain scale score, median (IQR)	5 (3-6)
Duration of hospitalization, median (IQR), d	4 (3-6)
Post ESD electrocoagulation syndrome	
Absent	18 (35.3)
Mild	24 (47.1)
Severe	9 (17.6)

SD: Standard deviation; IQR: Interquartile range; BT: Body temperature; WBC: White blood cell.

the endoscope in all cases. To identify the target lesion, chromoendoscopy with Lugol's stain or narrow band imaging with magnification was used. The area around the lesion was marked with electrical coagulation. A mixture of 10% glycerol solution and 0.005 mg/mL epinephrine was injected through a 25-gauge needle into the submucosal layer under the lesion. In some cases, hyaluronic acid (Endo-Mucoup; BMI Korea, Jeju, South Korea) was added to the mixture. An endoscopic carbon dioxide regulation unit (UCR, Olympus, Tokyo, Japan) was used for the insufflation. A dual knife (KD-650Q; Olympus) or an IT-knife 2 (KD-610L; Olympus) was used to perform the submucosal dissection with the Swift coagulation mode of an electrosurgical generator (VIO 300D; Erbe Elektromedizin GmbH, Tübingen, Germany). Hemostatic forceps (Coagrasper, FD-410LR;

Olympus) with a soft coagulation mode (60-W output) were used to control bleeding during the procedure (Figure 2).

After ESD, the patients were closely observed to detect any adverse events. Intravenous proton pump inhibitors and oral sucralfate were administered to each patient to prevent procedure-related bleeding. Chest and abdominal X-rays were taken immediately at the end of the procedure and the following morning to identify any leakage of luminal air or pneumonic consolidation. On the day following the procedure, complete blood cell count was performed to evaluate the leukocytosis. If any aspiration or minute perforation was suspected during ESD, prophylactic antibiotics were administered to the patients. In the absence of evidence of complications such as bleeding or perforation, a clear liquid diet was served the following morning and the patient was discharged in two or three days.

Statistical analysis

Categorical data were analyzed using Fisher's exact test or the χ^2 test. Student's *t*-test or the Mann-Whitney *U* test was used for analysis of quantitative data. Receiver operating characteristic (ROC) curve analysis was performed to find the optimal cutoff values of quantitative data such as resected area and procedure time. In the univariate analysis to determine independent risk factors for PEECS, variables with *P* < 0.05 were considered statistically significant and were added to the multivariate logistic regression. All statistical analysis was performed using SPSS software, version 18.0 for Windows (SPSS, Chicago, IL, United States).

RESULTS

We obtained data from 55 consecutive patients with SEN treated by ESD at Gangnam Severance Hospital. Among them, 4 patients were excluded because of procedure-related complication (3 cases of perforation, 1 case of bleeding). Thus, 51 patients were enrolled in our study. Table 1 shows the patient and tumor baseline characteristics. Most of the patients were male (46, 90.2%), and the mean age was 63.6 years. According to the Paris classification scheme, the tumors of 40 patients (78.4%) had type 0-IIb gross appearance. There were 14 patients (27.5%) who had dysplasia and 37 patients (72.5%) who had squamous cell carcinoma. Regarding tumor invasion depth, 38 cases (74.5%) had mucosal invasion and 13 cases (25.5%) had submucosal invasion. More than half of the patients had no muscle fiber exposure after the procedure (52.9%). The median resected area was 4.5 cm^2 (range 0.8-17.6) and the median procedure time was 40 minutes (range 17-167). The median WBC after the procedure was 10800 cells/uL. There were 2 patients who had a fever (≥ 37.8 ℃) without any obvious evidence of infection. There were 8 patients (15.7%) who had severe pain (≥ 6 points) after ESD. As a result, 24 patients

Table 2 Univariate analysis of risk factors for post endoscopic submucosal dissection electrocoagulation syndrome *n* (%)

	No PEECS (*n* = 18)	PEECS (*n* = 33)	*P* value
Male sex,	17 (94.4)	29 (87.9)	0.451
Age, mean ± SD, yr	63.6 ± 11.2	63.6 ± 8.5	0.977
Comorbidity			0.769
Absent	9 (50.0)	19 (57.6)	
Present	9 (50.0)	14 (42.4)	
Gross appearance			0.933
Flat	14 (77.8)	26 (78.8)	
Non-flat	4 (22.2)	7 (21.2)	
Location			0.378
Upper and middle	10 (55.6)	13 (39.4)	
Lower and EGJ	8 (44.4)	20 (60.6)	
Circumferential extension, median (IQR), %	35 (30-42.5)	40 (30-60)	0.164
Pathology			0.487
Dysplasia	6 (33.3)	8 (24.2)	
Squamous cell carcinoma	12 (66.7)	25 (75.8)	
Invasion depth			0.082
Mucosa	16 (88.9)	22 (66.7)	
Submucosa	2 (11.1)	11 (33.3)	
Resected area			0.035
< 6.0 cm^2	15 (83.3)	17 (51.5)	
≥ 6.0 cm^2	3 (16.7)	16 (48.5)	
Procedure time			0.026
< 25 min	7 (38.9)	4 (12.1)	
≥ 25 min	11 (61.1)	29 (87.9)	
Muscle layer exposure			0.018
Absent	14 (77.8)	13 (39.4)	
Present	4 (22.2)	20 (60.6)	
Hospitalization period, mean (IQR), d	3.5 (3-4)	5 (4-6)	0.007
Antibiotics use			0.020
No	14 (77.8)	14 (42.4)	
Yes	4 (22.2)	19 (57.6)	

PEECS: Post endoscopic submucosal dissection electrocoagulation syndrome; SD: Standard deviation; EGJ: Esophagogastric junction; IQR: Interquartile range.

(47.1%) developed mild PEECS and 9 patients (17.6%) developed severe PEECS during the post-ESD period.

There were several significant differences between patients with *vs* patients without PEECS. Patients with PEECS had a relatively larger resection area, a longer mean procedure time, a more often incidence of proper muscle layer exposure, a more prolonged hospitalization period, and a more frequent administration of antibiotics. However, patient-related factors (sex, age, comorbidity) and tumor-related factors (gross appearance, tumor location, tumor histology, tumor invasion depth) were not significantly associated with the development of PEECS (Table 2). Also, ESD learning curve did not show statistically significant relationship with PEECS. The difference in PEECS incidence among the operators was not statistically significant (55.8% *vs* 50%, *P* = 0.529). Multivariate analysis revealed that a resection area larger than 6.0 cm^2 (OR = 4.995, 95%CI: 1.110-22.489, *P* = 0.036) and a present of muscle layer exposure (OR = 5.661, 95%CI: 1.422-22.534, *P* = 0.014) were independent risk factors for PEECS (Table 3). We did not include hospitalization period and antibiotics use in the multivariate analysis, because these factors are considered as consequence of the PEECS rather than cause. No patient diagnosed with PEECS required additional surgery and all patients diagnosed with PEECS spontaneously recovered with intravenous hydration and antibiotics.

DISCUSSION

While ESD is a feasible and effective method for the treatment of SEN, it is a technically difficult procedure and its complications remain a problem[18]. Pain, bleeding, and perforation are common acute complications after esophageal ESD[19]. In addition to major complications, various minor complications may accompany this procedure. These complications, such as chest discomfort, nausea, vomiting, and pyrexia, tend to occur frequently in the postesophageal ESD period. We define esophageal PEECS as a condition accompanied by fever, systemic inflammatory response and chest pain after ESD without such perforation. There have been previous studies on PEECS for Gastric ESD and Colonic ESD[13,20]. The present study is the first to focus on PEECS in the esophagus, which was characterized by fever, leukocytosis, or regional chest pain.

The incidence of esophageal PEECS in this study was higher (60.8%) than the incidence of PEECS in the colon in previous studies[11,12]. This relatively high incidence may have several explanations. Firstly, the esophagus lacks a serosal membrane, unlike other gastrointestinal

Table 3 Multivariate logistic regression analysis of risk factors for post endoscopic submucosal dissection electrocoagulation syndrome

Factor	OR (95%CI)	*P* value
Procedure time		0.379
⩽ 25 min	Reference	
> 25 min	2.032 (0.419-9.868)	
Resected area		0.036
⩽ 6.0 cm^2	Reference	
> 6.0 cm^2	4.995 (1.110-22.489)	
Muscle layer exposure		0.014
Absent	Reference	
Present	5.661 (1.422-22.534)	

tract organs. Instead of a serosal membrane, the esophagus has a unique structure called adventitia, which is composed of loose connective tissue. Due to the lack of a serosal layer in the esophageal wall, the esophagus might be more susceptible to PEECS than the colon. Moreover, many important organs surround the esophagus, such as the aorta and the bronchus. We propose that these anatomical differences may affect the development of esophageal PEECS. Secondly, although we proposed a definition of esophageal PEECS for this study, a definitive definition of PEECS has not yet been established. While the definition of post polypectomy coagulation syndrome was first published in the 1980s, the criteria were ambiguous and no exact value has been proposed[21]. Moreover, previous studies on gastric or colorectal PEECS also used slightly different definitions[11-13]. These discrepancies may affect relatively high incidence of the PEECS.

In this study, 2 risk factors - resection area and muscle layer exposure - were identified for PEECS in esophageal ESD. These findings are slightly different from previous studies. For instance, polyp size and location were found to be risk factors of post polypectomy electrocoagulation syndrome in the colon[22,23]. For colorectal PEECS, female sex, tumor location, piecemeal resection, tumor size, and procedure time have been identified as risk factors[11,12]. In gastric ESD, tumor size, location, and procedure time have been identified as risk factors for PEECS[13]. While sex differences might influence pain perception, most of the patients with SEN were male[6,17,18,24]. Therefore, it is difficult to identify differences in the incidence of PEECS due to sex based on the data in the present study. In colon ESD, PEECS has been shown to be more common in the right colon than the left colon because of anatomical differences[12,23]. However, unlike the colon, anatomical variation according to the location in the esophagus did not significantly affect the occurrence of PEECS.

PEECS occurred more often with wide resection areas, most likely because the wide area meant that more electric cauterization was required[11,12]. Also, the muscle layer exposure affected the development of

PEECS in this study. In colon ESD, superficial damage of the muscularis propria does not significantly influence the spread of inflammation[11]. However, the esophagus does not have serosa membrane, and exposure of bare muscle fibers may have an effect on the propagation of inflammatory substances through muscularis propria. For complete resection of the tumor, clinicians usually attempt to dissect the submucosal layer as deeply as possible to the extent that it does not damage the muscular layers of the esophagus. Therefore, muscle layer exposure can occur frequently during the procedure, and it can be expected that it would have a significant impact on the occurrence of PEECS. The longer procedure time, the chance of fluid aspiration to the respiratory tract may increase substantially. Although longer procedure time was significantly associated with PEECS in univariate analysis, the multivariate analysis showed that longer procedure time was not an independent risk factor of esophageal PEECS. Kawata *et al*[25]. reported an incidence of bacteremia after esophageal ESD of 1%. Due to the rare incidence of bacteremia, they did not recommend prophylactic antibiotics for patients who undergo esophageal ESD. In our study, we used antibiotics only when patients were suspected to have complications. All patients with PEECS showed good outcomes without any severe complications. As a result, we suggest that esophageal PEECS is a systemic inflammatory response syndrome caused by electrical burns and transmural penetration of oro-esophageal secretion rather than true infection.

There are several limitations of our study. First, it was a small number and retrospective study that was performed at a single center. Thus, the cut off values we have established need external validation. Furthermore, there may be a recording bias because of retrospective design. Second, assessment of pain felt by patients after ESD may be subjective because pain tolerance can vary according to sex or age[17]. Third, we routinely perform chest and abdomen X-ray examinations after esophageal ESD. A computed tomography (CT) scan might be needed to detect micro perforations accurately after ESD. However, we performed a CT scan only when perforation was suspected on X-ray scans. Even if micro perforations were present, all patients in our study showed improvement with conservative treatment.

This is the first study of PEECS for esophageal lesions. PEECS is a common clinical syndrome characterized by chest pain, leukocytosis, or fever after esophageal ESD. It is another kind of clinical syndrome that is different from systemic inflammatory response syndrome. However, PEECS can be easily controlled by conservative management without surgical intervention when there is no obvious perforation. We found that the incidence of PEECS was high when the resected tumor area exceeded 6.0 cm^2 or when the muscle layer exposure was present. If these risk factors are accompanied, careful attention should be paid to the

potential occurrence of PEECS after esophageal ESD.

ARTICLE HIGHLIGHTS

Research background

A number of patients experience fever, chest pain, and/or a systemic inflammatory response after esophageal endoscopic submucosal dissection (ESD), even in the absence of obvious perforation.

Research motivation

Post ESD electrocoagulation syndrome (PEECS) is known as a common complication after colon ESD. However, there were no studies of PEECS after esophageal ESD.

Research objectives

We aimed to investigate the incidence and risk factors of PEECS in the esophagus.

Research methods

We retrospectively analyzed electronic medical database of patients who underwent esophageal ESD for superficial esophageal squamous neoplasms between March 2009 and December 2016 at single center in South Korea. PEECS was defined as meeting one of following criteria: fever ($\geq$ 37.8 ℃), leukocytosis (> 10800 counts/μL), or regional chest pain greater than 5/10 points as assessed on a numeric pain rating scale within 24 h after ESD.

Research results

As a result, 24 patients (47.1%) developed mild PEECS and 9 patients (17.6%) developed severe PEECS during the post-ESD period. We identified that that a resection area larger than 6.0 cm^2 (OR = 4.995, 95%CI: 1.110-22.489, P = 0.036) and a present of muscle layer exposure (OR 5.661, 95%CI: 1.422-22.534, P = 0.014) were independent risk factors for PEECS. All patients diagnosed with PEECS fully recovered with conservative management, such as intravenous hydration and antibiotics.

Research conclusions

PEECS is not a rare clinical after esophageal ESD. However, PEECS can be easily controlled by conservative management without surgical intervention when there is no obvious perforation. We conclude that the incidence of PEECS is expected to be high when the resected tumor area exceeds 6.0 cm^2 or when the muscle layer exposure is present.

Research perspective

If these risk factors are accompanied, careful attention should be paid to the potential occurrence of PEECS after esophageal ESD. Further large-scale study is needed to validate our research.

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