Polyglycolic acid sheet application to prevent esophageal stricture after endoscopic submucosal dissection for esophageal squamous cell carcinoma

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Background and study aim: Esophageal stricture following endoscopic submucosal dissection (ESD) can be a serious complication in patients with large mucosal defects. This preliminary study examined the efficacy of using a polyglycolic acid (PGA) sheet with fibrin glue for the prevention of esophageal stricture after ESD.

Patients and methods: A total of 15 patients were enrolled. After resection, PGA sheets were placed over the surgical wound. The size of the mucosal defect was estimated by dividing the circumference of the esophagus into 12 parts of equal size. The occurrence of esophageal stricture at 6 weeks, along with the proportion of patients who had PGA sheet remaining in place 1 week and 2 weeks after ESD, and the occurrence of adverse events were investigated.

Results: The size of mucosal defects in the 15 patients were 7/12 (n=4), 8/12 (n=5), 9/12 (n=4), 10/12 (n=1) and 11/12 (n=1). Esophageal stricture occurred in 1/13 patients (7.7%; two patients were not included in the analysis because they had required surgical resection during the follow-up period). The PGA sheet remained at 1 week after ESD in 13/15 patients (86.7%) and at 2 weeks after ESD in 6/15 patients (40%). No adverse events were observed.

Conclusion: PGA sheets may have the potential to prevent esophageal stricture.

Introduction

With advances in endoscopic treatment for superficial esophageal cancer, endoscopic submucosal dissection (ESD) now enables larger lesions than previously to be resected en bloc, including lesions that were previously considered beyond the indications for endoscopic resection. However, esophageal stricture is a major complication that can occur following ESD in patients left with large mucosal defects and this can lead to a poorer quality of life (QOL). Some reports have shown that the incidence of stricture is 70%–90% in patients left with a mucosal defect occupying more than three-quarters of the esophageal circumference [1–3]. The risk of stricture formation in relation to the circumference and length of the resection area was summarized by Chung et al. [4], although the lesions in their study were located only in the lower esophagus.

Post-ESD stricture substantially decreases QOL and can require multiple endoscopic balloon dilations (EBDs). Furthermore, patients with post-ESD stricture require frequent hospital visits, experience pain and discomfort during or after EBD, and sometimes develop further complications due to EBD. Therefore, formation of a post-ESD stricture contributes to the disadvantages of the treatment, including a reduced QOL and increased medical costs.

The efficacy of prophylactic steroids for preventing post-ESD stricture has recently been reported, but the route of administration remains controversial: injection of steroid into an artificial ulcer was reported to decrease the frequency of both post-ESD stricture and the need for EBDs [1], but the same has been reported for oral administration of prednisolone [5]. It should be noted, however, that delayed perforation after injection of steroid has also been reported as a direct complication [6]. In our current situation with increasingly elderly patients being treated, adverse events after steroid use are of great concern, and therefore, a safer and more effective preventive method is desirable.

According to previous reports, a polyglycolic acid (PGA) sheet (Neoveil, Gunze Co., Kyoto, Japan) with fibrin glue (Bolheal, Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan; or Beriplast P combi-set, CSL Behring Pharma, Tokyo, Japan) can prevent scarring and contraction after partial glossectomy [7–9]. The PGA sheet is an

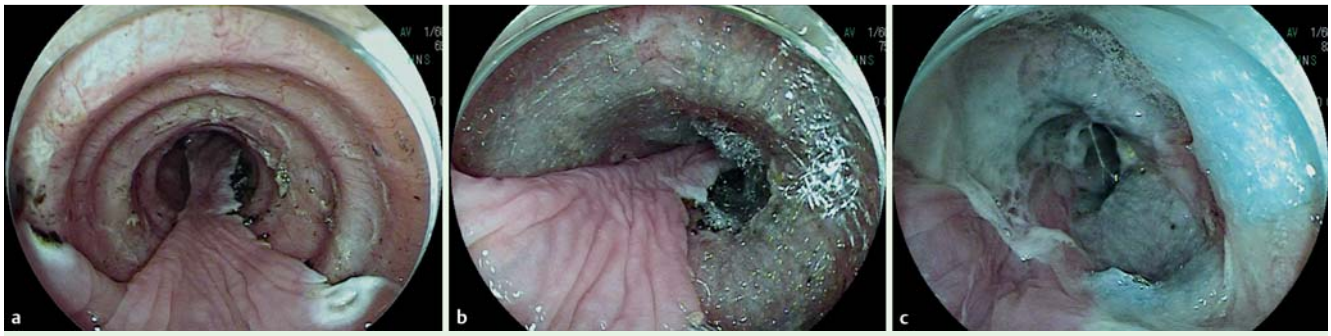

Fig. 1 Endoscopic views showing: **a** an artificial ulcer immediately after esophageal endoscopic submucosal dissection (ESD); **b** the polyglycolic acid (PGA) sheet that has been placed to cover the artificial ulcer; **c** the appearance of the ulcer covered by the PGA sheet after spraying with fibrin glue.

absorbable suture stiffener, so methods involving PGA sheets and fibrin glue to cover wounds, known as the "mucosal defect covered with fibrin glue and PGA sheet" (MCFP) technique [9], have been applied in many fields of surgery and appear to be safe [10, 11].

We hypothesized that covering a mucosal defect after ESD using the MCFP technique would prevent esophageal strictures. We therefore examined the efficacy of the MCFP technique for the prevention of esophageal stricture formation after ESD for superficial esophageal cancer.

Patients and methods

Patients

A total of 104 patients underwent ESD for superficial esophageal cancer from May 2012 to August 2013. Of these, 15 patients were enrolled in the study after they had provided written informed consent. Inclusion criteria were: a preoperative assessment that the tumor depth was limited to the lamina propria layer and the assumption that the lesion would be more than half but less than the whole circumference of the mucosal defect after ESD. Exclusion criteria were: a history of esophagectomy or radiation therapy, a lesion determined on endoscopy to be located near a scar left after previous endoscopic resection, a lesion that was suspected preoperatively to be m3 or sm1 disease, uncontrolled diabetes mellitus, and current steroid hormone use.

ESD procedure

An EG450-RD5 endoscope (Fujifilm Medical Co., Ltd., Tokyo Japan) and a dual knife (Olympus Optical Co., Ltd., Tokyo, Japan) were used for ESD. Glyceol with small amounts of indigo carmine and epinephrine was used for injection, and an ICC200 high-frequency generator (Erbe, Tübingen, Germany) was used for radiofrequency ablation.

The extent of the lesion was identified by spraying iodine under white-light observation, and dots were marked around the lesion. The lesion was lifted by injecting Glyceol into the submucosal layer at the posterior end of the lesion, and submucosal dissection was performed. Next, the same procedure was performed at the anterior end of the lesion. Submucosal dissection was then completed in the posterior direction and the lesion was resected en bloc. Exteriorized small vessels were treated by a hemostatic procedure, and a submucosal injection was given if necessary during submucosal dissection.

The resected specimen was extracted, fixed in formalin, and cut into 2-mm slices to investigate the invasion depth and tumor margin, and for lymphovascular involvement.

MCFP technique

The size of the mucosal defect (**Fig. 1a**) was calculated by dividing the circumference into 12 parts of equal size. PGA sheets were then cut into patches measuring 15×7 mm. The first step was to spray a small amount of the fibrinogen solution from the fibrin glue (Bolheal or Beriplast P) onto the artificial ulcer. The PGA sheet patches were then placed without overlapping onto as much as possible of the area of the large circumferential mucosal defect by roughly estimating their position based on the circumference and length of the defect (**Fig. 1b**). The fibrinogen and thrombin solutions of the fibrin glue were then sprayed onto the PGA sheet patches (**Fig. 1c**).

The subsequent dietary program was as follows: a fasting period after ESD of 2 days; resumption of oral feeding once the patient had been observed for 2 days without evidence of complications, consisting of liquid feeding for 2 days, which was then followed by a change to a solid diet. The solid diet was continued during the 6-week follow-up period. No proton pump inhibitors were administered to any patients.

Follow-up and evaluation

Endoscopic examination was performed 1, 2, 4, and 6 weeks after ESD, with the presence of the PGA sheet being recorded at 1 week and 2 weeks and the artificial ulcer being checked for scar formation at 6 weeks. The proportion of patients who had PGA sheet remaining in place 1 week and 2 weeks after ESD (**Fig. 2a**), the prevalence of esophageal stricture at 6 weeks (**Fig. 2b**), and the occurrence of adverse events were all recorded.

Results

The characteristics of the 15 patients (13 men, 2 women; mean age 68.6) are shown in **Table 1**. Lesions were located in the mid-esophagus in 10 patients and in the lower esophagus in five patients. Two patients who were diagnosed histologically as having m3 and sm2 disease, who had mucosal defects of 7/12 and 9/12, subsequently underwent surgical resections at 30 days and 20 days after ESD, respectively. They were therefore excluded from the analysis of esophageal stricture formation at 6 weeks.

Esophageal stricture at 6 weeks after ESD occurred in 1/13 patients (7.7%), and no new esophageal strictures were observed

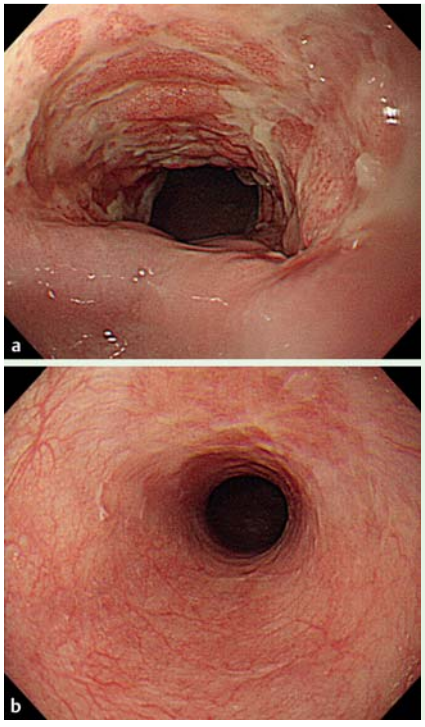

Fig. 2 Endoscopic views showing the appearance of the treated area: **a** 2 weeks after endoscopic submucosal dissection (ESD), with a mix of red areas that had been covered by the polyglycolic acid (PGA) sheet and white areas that were not covered; **b** 11 weeks after ESD, with good healing and no evidence of esophageal stricture formation.

over the median follow-up period of 352 days (range 60 – 535 days). Symptomatic dysphagia developed in three patients. Two of them became aware of dysphagia only a few days after the ESD; however, it was still possible to easily pass the endoscope through their ESD scars. In the third patient who was aware of dysphagia (dysphagia score of 1 [12]), an esophageal stricture that did not allow the H260 endoscope (Olympus Optical Co.) to be passed through the ESD scar had developed by 4 weeks after the procedure. This stricture was finally released after performing balloon dilation five times.

The PGA sheet remained in 13/15 patients (86.7 %) 1 week after ESD and in 6/15 patients (40 %) 2 weeks after ESD. No adverse events such as infection or allergic reaction were observed. As a minor complication, post-ESD bleeding occurred in one patient but this was managed successfully with conservative treatment and a blood transfusion was not required. No serious complications or treatment-related deaths were noted.

Discussion

PGA sheets have been applied to the duodenum [13] and colon [14] to prevent perforation or post-ESD bleeding. However, this is the first report to demonstrate the potential of the MCFP technique for the prevention of esophageal stricture. Given the low rate of occurrence of esophageal stricture in this study (7.7 %), the MCFP technique may be efficacious in preventing esophageal stricture after ESD. When treatment was limited to patients with a mucosal defect of more than two-thirds of the esophageal circumference, the prevalence of esophageal stricture was 10 % (1/10 patients), which is lower than that in previous reports [1 – 3]. In addition, as the cost of PGA sheets in the Japanese market is about one-third that of a dual knife, the financial burden on patients is low.

The mechanism preventing the development of esophageal stricture is not known because no basic studies in this area have been performed. However, in terms of the mechanism preventing contraction after partial glossectomy, it has been speculated that the PGA sheet and fibrin glue protect the wound surface from stimulation and indigenous bacteria in the mouth, meaning the inflammatory response is mild, which will result in less cicatrization [7].

With regard to the wound healing process, Kumar et al. [15] reported the following four steps: (i) an inflammatory response to exogenous material on the wound surface and organization of granulation tissue; (ii) proliferation of epidermal cells around the wound and covering of the granulation tissue surface with

Table 1 Clinical and tumor characteristics and outcomes of the 15 patients with superficial esophageal cancer who underwent endoscopic submucosal dissection (ESD) followed by coverage of the mucosal defect using a polyglycolic acid (PGA) sheet and fibrin glue.

Case number	Age, years; sex	Location in esophagus	Size of mucosal defect[1]	Histological invasion depth	PGA sheet remaining at		Esophageal stricture at 6 weeks
					1 week	2 weeks	
1	65; male	Middle	7	m1	No	No	No
2	79; male	Middle	8	m2	Yes	Yes	No
3	62; female	Middle	9	sm2	Yes	Not checked	N/A[2]
4	55; male	Lower	8	m2	Yes	Yes	No
5	65; male	Middle	8	m2	Yes	Yes	No
6	65; female	Middle	7	m2	Yes	No	No
7	79; male	Lower	8	m2	Yes	No	No
8	71; male	Lower	11	m2	Yes	No	No
9	72; male	Middle	7	m3	Yes	Yes	N/A[2]
10	54; male	Middle	9	m2	Yes	No	No
11	82; male	Lower	10	m2	Yes	No	No
12	75; male	Middle	9	m2	Yes	Yes	Yes
13	79; male	Lower	7	m1	Yes	Yes	No
14	54; male	Middle	9	m2	No	No	No
15	72; male	Middle	8	m2	Yes	No	No

N/A, not applicable.

[1] The size of the mucosal defect was measured as the proportion of the esophageal circumference that was occupied by the defect when the circumference was divided into 12 equal parts.

[2] A surgical resection was needed before the 6-week assessment.

these cells; (iii) growth of subepithelial granulation tissue to cover the defect within 7 days; and (iv) scar formation and contraction after maturation of the granulation tissue, such as differentiation from fibroblasts into fiber cells or contraction of collagen fibers. According to this theory, esophageal stricture in our study is prevented because the PGA sheet and fibrin glue protect the wound surface from contact with exogenous materials and subsequent organization of the granulation tissue. In fact, as shown in **Fig. 2a**, the parts of the defect covered by the PGA sheet became red, while other parts that were not covered by the PGA sheet developed a white coating. It remains necessary, however, to confirm the details of this hypothetical mechanism in an animal study.

The present procedure has a few technical limitations. The intricate technique took a long time for delivery of the PGA sheets to the surface of the artificial ulcer, probably because the sheets used in this study were small (15×7 mm). Therefore, it was necessary to repeatedly move the endoscope in and out. In fact, it took an average of 14 minutes (range 10–20 minutes) to patch the ulcer with the PGA sheets, although the procedure time was recorded in only the last eight patients because it had not initially been configured as a study endpoint. A mean of 10 PGA sheets were delivered.

Another issue arose was when the artificial ulcer was located on the upper aspect of the esophageal lumen as gravity made the procedure harder because the patched PGA sheet easily dropped off the defect. In addition, when peristalsis occurred, it was difficult to patch the defect with the PGA sheet. Furthermore, the constant movement of the endoscope in and out resulted in the PGA sheet easily becoming detached upon contact with the endoscope.

Recently, a new technique for delivering PGA sheets was described in a case report [16]. As our study was a prospective evaluation conducted before publication of this case report, our method of delivery was different from theirs. In their method, a PGA sheet covered the entire artificial ulcer and was held in place by clips. Therefore, the chance of leaving part of the ulcer uncovered may be smaller and the required time may be shorter compared with our method. In any case, our technique needs further refinement before it can be generalized.

Other limitations of this study were that both the total number of enrolled patients and the number of patients with a large mucosal defect were small. Therefore, a larger study involving more patients with mucosal defects covering at least three-quarters of the circumference is needed to confirm whether the PGA sheet plus fibrin glue is efficacious in preventing esophageal stricture. Furthermore, as this study is a preliminary investigation, a prospective trial comparing against patients treated with steroid administration or balloon dilation should be conducted. No histological investigations have been performed on the mechanism preventing esophageal stricture; therefore, it is also necessary to investigate whether it is the PGA sheet, the fibrin glue, or a synergistic effect that is efficacious.

In conclusion, treatment with a PGA sheet and fibrin glue reduced the number of esophageal strictures following ESD and appears to be a safe procedure. PGA sheets appear to be a promising material for the prevention of esophageal stricture.

Competing interests: None

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