

CASE REPORT

Nagoya J. Med. Sci. 85. 134–140, 2023
doi:10.18999/nagjms.85.1.134

Successful prevention of stenosis after circumferential endoscopic resection of esophageal cancer

Hitoshi Tanaka, Naomi Kakushima, Koichi Muroi, Takashi Hirose, Tomohiko Suzuki, Takahiro Suzuki, Emiko Hida, Keiko Hirai, Hiroyuki Shibata, Nobuhito Ito, Satoshi Furune, Kazuhiro Furukawa and Mitsuhiro Fujishiro

Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Circumferential resection of a >5-cm longitudinal mucosal defect following esophageal endoscopic submucosal dissection (ESD) is a risk factor for refractory stenosis. Circumferential ESD was performed in 3 patients with 64, 69, and 70 mm longitudinal mucosal defects. A local steroid injection was used to treat the postoperative ulcer, followed by an oral steroid. In all three cases, the ulcer healed without the need for endoscopic dilation. A combination of local injection and oral steroids effectively prevented esophageal stenosis in patients with high-risk stenosis after ESD.

Keywords: endoscopic submucosal dissection, esophagus, stenosis

Abbreviations:

ESD: endoscopic submucosal dissection

PGA: polyglycolic acid

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely used to treat early-stage esophageal cancer.¹ However, while treating widespread lesions with ESD, post-ESD stenosis is a serious complication. Endoscopic balloon dilation and steroid administration have been reported to reduce the incidence of stenosis; however, these preventive measures are not standardized. Moreover, refractory stenosis occurs in cases where circumferential resection of a >5-cm longitudinal mucosal defect is performed.²

We herein report three cases of circumferential ESD of a >5-cm longitudinal mucosal defect for a widespread lesion, in which stenosis was prevented using a combination of a local steroid injection and an oral steroid.

Received: December 15, 2021; accepted: February 24, 2022

Corresponding Author: Naomi Kakushima, MD, PhD

Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2172, Fax: +81-52-744-2180, E-mail: nk202004@med.nagoya-u.ac.jp

CASE REPORT

Case 1

A man in his 60's underwent ESD for a circumferential 0-IIc lesion located in the middle thoracic esophagus (25–30 cm from incisura) (Fig. 1A). A Splash-M knife® (HOYA Corp, Pentax, Tokyo, Japan) was used for ESD. Successful en bloc resection was performed without any complications (Fig. 1B). The excised specimen measured 64 mm in length, and a circum-

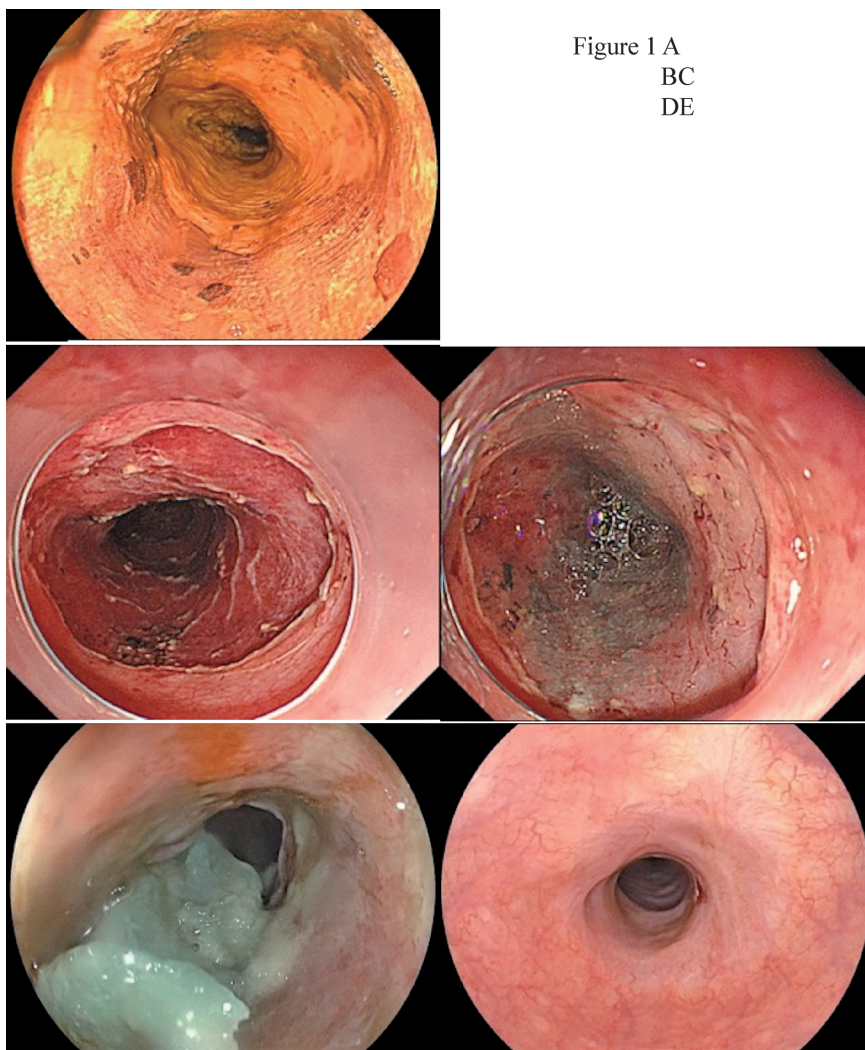


Figure 1 A
BC
DE

Fig. 1 Case 1

Fig. 1A: A circumferential 0-IIc lesion in the middle thoracic esophagus.

Fig. 1B: Endoscopic submucosal dissection (ESD) was performed without complications, and a circumferential ulcer was observed at 25–33 cm from the incisura.

Fig. 1C: After local injection of 80 mg of triamcinolone acetonide, a polyglycolic acid (PGA) sheet covering was performed.

Fig. 1D: One week after ESD, the PGA sheet almost fell off at the anal side of the ulcer.

Fig. 1E: At 8 weeks, a circumferential scar was observed, and the endoscope passed through without resistance.

ferential ulcer was observed at 25–33 cm from the incisura. For the ulcer caused by ESD, 80 mg of triamcinolone acetonide dissolved in saline was injected into the residual submucosal tissue in 1–2 mg increments. After injection, the ulcer was covered with a polyglycolic acid (PGA) sheet (Neoveil, Gunze Co, Kyoto, Japan) with fibrin glue (Beriplast P combi-set, CSL Behring Pharma, Tokyo, Japan) (Fig. 1C). On postoperative day 2, a soft meal was introduced, along with 30 mg of oral prednisolone, which was gradually reduced by 5–10 mg/week over 8 weeks. Pathological examination revealed a moderately differentiated squamous cell carcinoma, pT1a-LPM, ly0, v0, 60 mm, with negative carcinoma margins. Esophagoscopy performed 1 week after ESD revealed that the PGA sheet had almost fallen off the ulcer caused by ESD (Fig. 1D). The patient experienced mild dysphagia during the post-ESD course, but he ate normal food. At 8 weeks after ESD, esophagoscopy revealed complete scarring of the ulcer and passage of the endoscope (9.9 mm diameter) through the lumen (Fig. 1E). Endoscopic dilation was not required during the pos-ESD course.

Case 2

A man in his 60's underwent ESD for a circumferential 0-IIc lesion located in the lower thoracic esophagus (31–37 cm from incisura) (Fig. 2A). Successful en bloc resection was per-

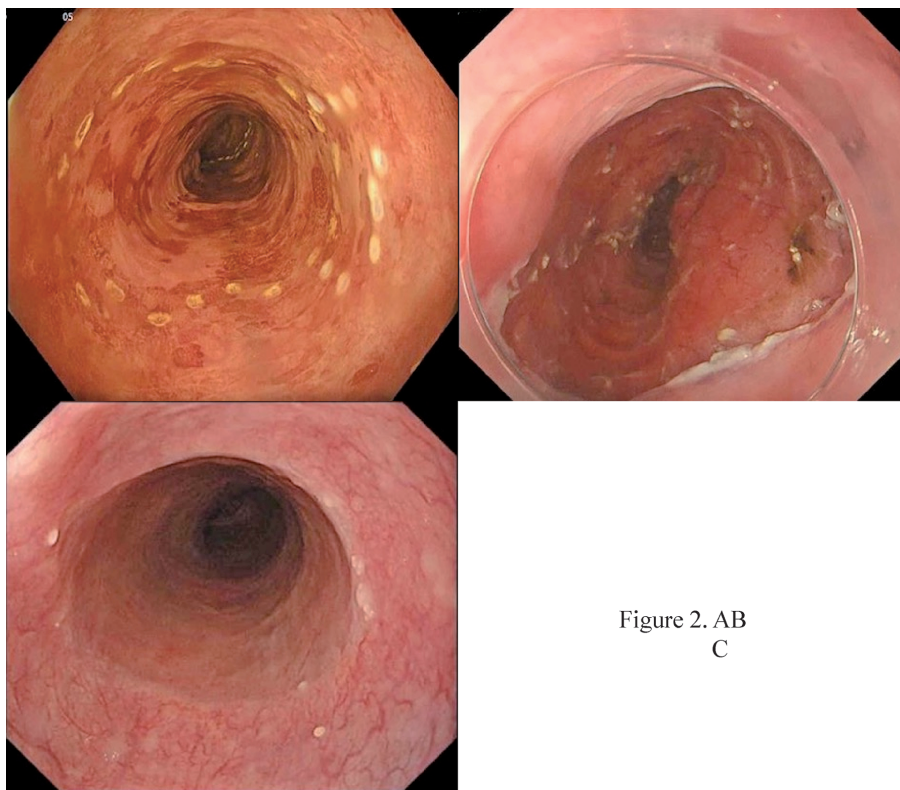


Figure 2. AB
C

Fig. 2 Case 2

Fig. 2A: A circumferential 0-IIc lesion in the lower thoracic esophagus.

Fig. 2B: ESD was performed without complications, and a circumferential ulcer was observed at 31–39 cm from the incisura.

Fig. 2C: At 8 weeks, a circumferential scar was observed, and the endoscope passed through without resistance.

formed without any complications (Fig. 2B). The excised specimen measured 69 mm in length, and a circumferential ulcer was observed at 31–39 cm from the incisura. To treat the ulcer caused by ESD, 80 mg of triamcinolone acetonide was injected immediately after the procedure, and 30 mg of oral prednisolone was started on postoperative day 2 as in case 1. Pathological examination revealed well-differentiated squamous cell carcinoma, pT1a-LPM, ly0, v0, 55 mm, with negative carcinoma margins. The patient did not have any symptoms during the post-ESD course, and complete scarring of the ulcer was observed at 8 weeks without stenosis (Fig. 2C).

Case 3

A man in his 50's underwent ESD for a circumferential 0-IIc located in the lower thoracic esophagus (30–35 cm from the incisura) (Fig. 3A). Successful en bloc resection was performed without any complications (Fig. 3B). The excised specimen measured 70 mm in length, and a circumferential ulcer was observed at 30–37 cm from the incisura. The patient received a local injection of 80 mg of triamcinolone acetonide and 30 mg of oral steroid as in cases 1 and 2. Pathological examination revealed a well-differentiated squamous cell carcinoma, pT1a-LPM, ly0, v0, 60 mm, with negative carcinoma margins. The patient did not have any symptoms during the post-ESD course, and complete scarring of the ulcer was observed at 8 weeks without stenosis (Fig. 3C).

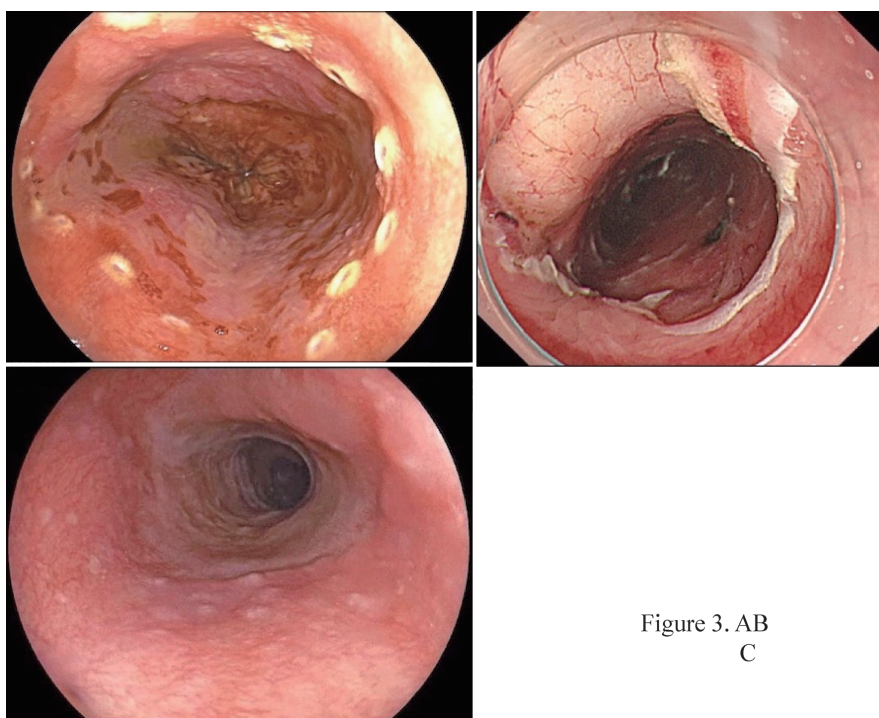


Figure 3. AB
C

Fig. 3 Case 3

Fig. 3A: A circumferential 0-IIc lesion in the lower thoracic esophagus.

Fig. 3B: ESD was performed without complication and a circumferential ulcer was observed at 30–37 cm from the incisura.

Fig. 3C: At 8 weeks, a circumferential scar was observed, and the endoscope passed through without resistance.

DISCUSSION

The incidence of stenosis is high after an esophageal ESD of mucosal defects covering $\geq 3/4$ of the circumference of the esophagus.^{3,4} To prevent post-ESD stenosis, the use of local injection⁵ or oral steroids,⁶ balloon dilation,⁷ stentings,⁸ and PGA sheet covering⁹ has been reported; however, these methods are not standardized, and their effects are not fully characterized. Multiple sessions of preventive endoscopic balloon dilation (EBD) are required to prevent stenosis in high-risk patients. The optimal time to start EBD after ESD and the interval between EBD sessions are unknown. The use of steroid is known to reduce the incidence of stenosis; however, whether injection or oral steroid is better, or both, and the optimal amount of steroid required are unknown. Furthermore, even after using these preventive methods, stenosis after a total circumferential ESD is frequently intractable. One reason for this could be that after circumferential resection, the length of the ESD ulcer increases due to contraction of the muscularis mucosa of the remaining oral and anal side mucosa.

In the first case, a combination of local injection, oral steroid, and PGA sheet covering was used. Although a previous study reported that this method was less effective in preventing stenosis if the PGA had fallen off at 1 week after ESD,¹⁰ the PGA could provide cytoskeleton and carry medicine to accelerate cell repair and wound healing. Histopathological assessment in an animal study revealed that ulcers covered with the PGA sheet had a thick layer containing fibrin glue and necrotic substances, abundant newly formed blood vessels, and good granulation at 1 week after the surgery, without excessive inflammation, necrosis, or infection.¹¹ A local steroid injection has a risk of perforation.¹² Thus, it is preferable to avoid multiple injections during the post-ESD course. The combination of steroid injection and PGA has been explored in previous studies but was not fully effective.¹³ The use of a PGA sheet containing fibrin glue in combination with injection and oral steroid therapy has not been explored in previous studies. Therefore, further studies are required to confirm the effect of this triple combination therapy.

Kadota et al reported a stenosis rate of 71% in patients with an entire circumferential mucosal defect after ESD using a local injection of 50 mg of triamcinolone acetonide followed by an oral steroid.³ Yamaguchi et al reported a stenosis rate of 33% using an oral steroid for a longer period (16–18 weeks).¹⁴ Systemic steroid therapy for a long period has a risk of serious adverse events, such as infection.

In our previous study, the rate of post-ESD stenosis in patients with mucosal defects covering $\geq 3/4$ but not entire circumference tended to be higher after local steroid injection (40–80 mg) alone than after local steroid injection and oral prednisolone (61% and 33%, respectively).¹⁵ Those who did not receive any steroid treatment developed stenosis and were treated with EBD. Three patients with entire circumferential mucosal defect received only injection, and one patient with entire circumferential mucosal defect received 40 mg of local injection with an oral steroid. All these 4 patients developed stenosis that required multiple EBD (unpublished data). Therefore, we believe that both local injection and oral steroid are required for patients with a $\geq 3/4$ mucosal defect, and the amount of steroid is essential, especially in patients with an entire circumferential mucosal defect. A triamcinolone product available in our hospital contains 40 mg of the active ingredient in one vial; thus, we used two vials (80 mg) in the three cases presented here. The dose of oral prednisolone was initially set as 0.5 mg/kg/day. The common factors among the three cases reported here were the combination of 80 mg of triamcinolone acetonide injection followed by 8 weeks of oral steroid. Although the mechanism of steroids in preventing stenosis is not fully understood, the anti-inflammation effect is considered to be the critical factor. Local injection immediately following ESD would exert a strong anti-inflammatory effect to the locoregional area. The duration of effective blood concentration of triamcinolone

after intramuscular injection is 14–21 days¹⁶; however, the duration after submucosal injection is unknown. After esophageal ESD, the ulcer has less submucosal tissue and is more vulnerable to food and mucus. Therefore, the duration of the effect of local injection is thought to be much shorter. The combination of local and oral steroids would decrease the repetition of local injection and the period of oral steroids. We also believe that a higher dose as 80 mg of local injection effectively suppresses the immediate inflammatory response at the ulcer for a circumferential ESD of a >5-cm longitudinal mucosal defect.

In conclusion, although the role of PGA in the prevention of stenosis in circumferential ESD cases still needs to be elucidated, a combination of local injection and oral steroids may be a promising preventive measure.

CONFLICTS OF INTEREST

All authors have no conflicts of interest.

REFERENCES

- 1 Abe S, Iyer PG, Oda I, Kanai N, Saito Y. Approaches for stricture prevention after esophageal endoscopic resection. *Gastrointest Endosc.* 2017;86(5):779–791. doi:10.1016/j.gie.2017.06.025.
- 2 Miwata T, Oka S, Tanaka S, et al. Risk factors for esophageal stenosis after entire circumferential endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Surg Endosc.* 2016;30(9):4049–4056. doi:10.1007/s00464-015-4719-3.
- 3 Kadota T, Yoda Y, Hori K, et al. Prophylactic steroid administration against strictures is not enough for mucosal defects involving the entire circumference of the esophageal lumen after esophageal endoscopic submucosal dissection (ESD). *Esophagus* 2020;17(4):440–447. doi:10.1007/s10388-020-00730-z.
- 4 Yamamoto Y, Kikuchi D, Nagami Y, et al. Management of adverse events related to endoscopic resection of upper gastrointestinal neoplasms: Review of the literature and recommendations from experts. *Dig Endosc.* 2019;31(Suppl 1):4–20. doi:10.1111/den.13388.
- 5 Hashimoto S, Kobayashi M, Takeuchi M, Sato Y, Narisawa R, Aoyagi Y. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. *Gastrointest Endosc.* 2011;74(6):1389–1393. doi:10.1016/j.gie.2011.07.070.
- 6 Yamaguchi N, Isomoto H, Nakayama T, et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc.* 2011;73(6):1115–1121. doi:10.1016/j.gie.2011.02.005.
- 7 Ezoe Y, Muto M, Horimatsu T, et al. Efficacy of preventive endoscopic balloon dilation for esophageal stricture after endoscopic resection. *J Clin Gastroenterol.* 2011;45(3):222–227. doi:10.1097/MCG.0b013e3181f39f4e.
- 8 Wen J, Lu Z, Yang Y, et al. Preventing stricture formation by covered esophageal stent placement after endoscopic submucosal dissection for early esophageal cancer. *Dig Dis Sci.* 2014;59(3):658–663. doi:10.1007/s10620-013-2958-5.
- 9 Sakaguchi Y, Tsuji Y, Ono S, et al. Polyglycolic acid sheets with fibrin glue can prevent esophageal stricture after endoscopic submucosal dissection. *Endoscopy.* 2015;47(4):336–340. doi:10.1055/s-0034-1390787.
- 10 Iizuka T, Kikuchi D, Hoteya S, Kajiyama Y, Kaise M. Polyglycolic acid sheet and fibrin glue for preventing esophageal stricture after endoscopic submucosal dissection: a historical control study. *Dis Esophagus.* 2017;30(11):1–8. doi:10.1093/dote/dox053.
- 11 Takao T, Takegawa Y, Shinya N, Tsudomi K, Oka S, Ono H. Tissue shielding with polyglycolic acid sheets and fibrin glue on ulcers induced by endoscopic submucosal dissection in a porcine model. *Endosc Int Open.* 2015;3(2):E146–E151. doi:10.1055/s-0034-1391391.
- 12 Yamashita S, Kato M, Fujimoto A, et al. Inadequate steroid injection after esophageal ESD might cause mural necrosis. *Endosc Int Open.* 2019;7(2):E115–E121. doi:10.1055/a-0781-2333.
- 13 Hikichi T, Nakamura J, Takasumi M, et al. Prevention of stricture after endoscopic submucosal dissection for superficial esophageal cancer: a review of the literature. *J Clin Med.* 2020;10(1):20. doi:10.3390/jcm10010020.

- 14 Yamaguchi N, Isomoto H, Fukuda H et al. Preventing stenosis after circumferential and semi-circumferential esophageal ESD -effect of oral steroid administration [in Japanese]. *Stomach Intest.* 2013;48(9):1291–1302. doi:10.11477/mf.1403113919.
- 15 Muroi K, Kakushima N, Furukawa K et al. Effects of steroid use for stenosis prevention after endoscopic submucosal dissection for cervical esophageal cancer. *Int J Clin Oncol.* 2022;27(5):940–947. doi:10.1007/s10147-022-02139-3.
- 16 Kusama M, Sakauchi N, Kumaoka S. Blood concentration and urinary excretion rate following intramuscular injection of triamcinolone acetonide [in Japanese]. *Nihon Naibunpi Gakkai Zasshi.* 1970;46(6):654–658. doi:10.1507/endocrine1927.46.6_654.