Regenerative Therapy 18 (2021) 441–446

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Original Article

Transplantation of acellularized dermis matrix (ADM) plus fully covered metal stent to prevent stricture after circumferential endoscopic submucosal dissection of early esophageal cancer (with video)

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ARTICLE INFO

Article history:
Received 13 May 2021
Received in revised form
25 August 2021
Accepted 6 October 2021

Keywords:
Acellularized dermis matrix
Esophagus
Endoscopy

ABSTRACT

Backgroud and study aims: Esophageal stricture is a serious adverse event occurring after circular endoscopic submucosal dissection (ESD) involving the whole esophagus. However, there is still a lack of effectively preventive methods. The main purpose of this study is to evaluate the efficacy of application of acellularized dermis matrix (ADM) for the prevention of post-ESD esophageal stricture. The main objective of this study was to evaluate the use of decellularized dermal matrix (ADM) in the prevention of post-esophageal ESD strictures.

Patients and methods: A pilot, single-center, prospective study was conducted. The study enrolled seven patients who had high-risks with extended resection of developing post-ESD esophageal stricture. After undergoing ESD, we attached different size of ADM patches to the mucosal defects using titanium clips then fixed with a metal mesh stent. The stent covered with metal mesh was removed at the median time of 27 days after the endoscopic procedure. Follow-up and repeated outpatient endoscopic screening were performed at appropriate scheduled times.

Results: The average longitudinal diameter of the resected specimens was 58.3 mm (range 38–90 mm). There were three patients developing strictures postoperatively at a mean time of 87 days (range 42–140). The median number of postoperative endoscopic balloon dilatation (EBD) in patients with stenosis was 2 (range 2–9). There were no deaths during a median follow-up period of 6 moths (range 1–12).

Conclusions: This study was performed to assess the efficacy and safe method of relieving the severity of esophageal stricture after ESD through transplantation of ADM.

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Abbreviations: Endoscopic Submucosal Dissection, ESD.

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

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https://doi.org/10.1016/j.reth.2021.10.002
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1. Introduction

With the popularity of gastroscopes and the continuous updating of endoscopic equipment, more and more patients with esophageal lesions can be diagnosed and treated early under endoscopy. As a minimally invasive technique, the long-term effect of endoscopic mucosal dissection (ESD) is comparable to that of open surgery, making it a routine treatment for early gastrointestinal and submucosal tumors. Especially in the field of early esophageal cancer treatment, ESD has become increasingly mature, and has gradually become the first choice of most clinicians [1]. The specimens resected by ESD can be evaluated in various aspects. The specimens resected completely have tumor-free lateral and basal margins. This method will avoid any residual tumor tissue and local recurrence [2]. However, in the case of large esophageal lesions, stenosis of the lumen, poor wound healing and subsequent bleeding may occur after ESD. Especially in recent weeks or after total resection, the range of lesion rate is from 88% to 100% [3]. Therefore, the key to reduce the complications of ESD is to promote the repair of esophageal wounds and inhibit excessive scar proliferation.

2. Complications of ESD

A variety of ESD-related complications have been reported, including perforation and postoperative stenosis [4], and the occurrence of which can significantly affect patients' prognosis and quality of life (QOL). The exact incidence rate of post-procedural esophageal stricture remains to be determined by further studies. However, studies show that the location of the cervix, a tumor size greater than 3/4 of the circumference of the esophagus, as well as a longitudina tumorl diameter over 40 mm are closely related to the occurrence of ESD-related stenosis [3]. In particular, the incidence rate of stricture is known to significantly increase in proportion to the overall size of the target lesion and the circumferential size of the post-ESD mucosal defect [5].

3. Treatment and prevention of Post-ESD esophageal stricture

There are currently multiple strategies and methods to prevent post-ESD esophageal stenosis [6]. Although endoscopic balloon dilatation (EBD) can treat benign esophageal stricture, it still has the risk of perforation [7] meanwhile requires high treatment cost. Anti-inflammatory approaches can also be used as an option to prevent post-ESD esophageal stenosis, such as using endoscopic injections of local steroids or systemic steroids, as advocated by some authors. However, these methods have the potential to induce some additional complications including delay in wound healing, formation of ulcer and metabolic disturbance (hyperglycemia and osteoporosis) [8,9]. Other agents include N-acetylcysteine and mitomycin C, as shown in some studies, have a certain effect on preventing esophageal stricture, but there is no preliminary data to clearly prove their effectiveness [10]. Lizuka et al. also reported polyglycolic acid sheet and fibrin glue showing a certain effect on stricture prevention in a historical control study [11]. In 2018, Liao et al. successfully applied the technique of autologous esophageal mucosal transplantation in nine patients to prevent stenosis after ESD [12]. However, small pieces of autologous esophageal mucosa need to be obtained many times for one patient, and large-area grafts difficult to be obtained. All in all, as for post-ESD esophageal stricture prevention, the current methods still have respective defects, and there is still a need to explore a better and efficient way.

Although there have been various medical interventions to choose from for post-ESD esophageal stricture prevention, including repeated endoscopic balloon dilatation (EBD) expansion [12], temporary stenting [13], oral steroids [9] and local steroid injections [14], and recently emerging transplantion of autologous oral mucosal epithelial cell sheets [15–20]. Unfortunately, the results of these preventive measures in clinical use have not been satisfactory. There is also a lack of standard, accepted and effective treatment for the prevention of postoperative strictures in circumferential esophageal mucosal defects. There is also a lack of standard treatment on postoperative esophageal stenosis prevention with peripheral mucosal defects. New technology matrix scaffolding materials such as autologous oral mucosa or extracellular membranes have also been proposed for the treatment of esophageal strictures. However, this approach has not been widely used in clinical practice due to the complex process including oral mucosa collection, cell separation and culture.

Biomaterials contain the ability to promote cell attachment and regulate cell behavior. As a natural template of a biomaterial, extracellular matrix (ECM) plays a key part in regulating cell phenotype and function in development, homeostasis and response to injury because of its intrinsic biochemical and mechanical cues. The ECM can not only use its property of physical scaffold to protect the structural integrity of multicellular organisms from been destroyed, but also provide the required biochemical and biophysical signals for the survival, organization and differentiation of cells [21–25].

Recently, ADM transplantation has safely and effectively promoted esophageal re-epithelialization and prevented esophageal stricture in 7 Bama miniature pigs, semi-circumferential ESD was performed at the distal esophagus [26]. However, at present, this approach is rarely used in clinical practice, lacking in accurate and reliable clinical experience to prove its efficacy.

4. Patients/materials and methods

4.1. Patients

Seven patients with EEC expected to develop an above 3/4-circumference post-procedure artificial ulcer received ADM transplantation after the ESD at the endoscopic center of Taizhou Hospital, Linhai, Taizhou, China, from June 2019 to August 2019. This study has been approved by the Medical Ethics Committee of Taizhou Hospital of Zhejiang Province (approval number: X20190603).

4.2. Material used in the trial and its rationale

Biodegradable scaffold consisting of porcine acellularized dermis matrix (ADM) has gained regulatory approval for clinical use [27]. It has been approved that ADM (Mesh with round hole, 1 cm*3 cm*1 mm; by Unitrump Biotech, Shanghai; China food and drug administration number: 3640430) is a biodegradable material that has been shown to reduce scar contracture [28,29]. The mechanisms of its inhibition of scar formation include: (1) formating of a bio-physical barrier; (2) rapid coagulation, which compresses blood animal through the formation of an adhesive plug, activates the accumulation of coagulation factors and

accumulates platelets; (3) inhibiting the effects of fibroblasts and human fibrinogen; (4) producing more hyaluronic acid; and (5) promoting the growth of epithelial cells [23].

However, there lacks reports to estimate the efficacy of ADM in the prevention of esophageal stenosis after ESD. And the exact effectiveness of this material in preventing post-ESD esophageal stenosis still lacks the support of pre-clinical experiments and clinical data.

4.3. ESD procedure

An endoscope (GIF-Q260J, Olympus, Tokyo, Japan) with a transparent cap attached to its tip, a dual knife (NM-400U-0423, Olympus), a hook knife (KD-620 LR, Olympus), an insulated-tip knife-2 (KD-611 L, Olympus), as well as hemostatic forceps (FD-410 LR, Olympus) were used in the ESD procedure. VIO200D (ERBE ELEKTROMEDIZIN GMBH, Germany) were used to incise the mucosal layer.

The ESD procedure for all patients was as follows:(1) after entering the esophageal cavity, use the endoscope with a water jet system to flush the entire esophageal cavity, (2) observe the overall esophageal mucosa to confirm the lesion location, the depth and extent of the lesion with white-light endoscopy and magnifying narrow-band imaging endoscopy (NBI); (3) Spray the whole esophageal mucosa with 1.5% Lugol's solution for iodine staining to clarify he extent of the lesion again; (4)use the Dual knife to make circumferential marks at least 5 mm outside the tumor margin; (5) inject a solution of 10 mL saline solution, 2.5 mL sodium hyaluronate, and 0.5 mL methylene blue into the submucosal layer to elevate the lesion, making it easier for dissection; (6) incise the mucosa around the marks with a Dual knife and then perfome ESD procedure with a hook knife or IT-2 knife.

We performed ADM graft transplantion rapidly after ESD. The procedure was as follows: (1) select appropriate ADM membranes depending on the size of the mucosal defect. When the width of the mucosal defect <4 cm, choose a 1 cm*2 cm membrane, when >4 cm, choose two 1 cm*3 cm membranes to be placed as shown in Fig. 1; (2) trim a ADM membrane into a rectangle and soak it in sterile saline solution for 300 s; (3) transport it to the ulcer with endoscopic forceps.; (4) use 6 to 8 metal clips (Olympus, Tokyo, Japan) to fix the graft and the ulcer bed edge to make them adhere tightly; (5) measure the length of the mucosal defect, then select an appropriate fully covered esophageal metal stent (CZES-II; Sigma, Zhejiang, China) which were required to cover at least 8.5 cm of both the oral and anal side of the mucosal defect.

4.4. Postoperative management

Postoperative observations included recording of complaints of abdominal/chest pain, dyspnea, abdominal distention, changes in vital signs, and an abdominal/chest examination. If there were no complications, an oral diet was suspended for 1 day after the procedure. Esomeprazole (40 mg twice daily, AstraZeneca, Sodertalje, Sweden) was administered intravenously during the patient's hospital stay and then orally for another 8 weeks. If mediastinal emphysema or pneumothorax was found during or after the procedure, conservative treatments, including the intravenous infusion of esomeprazole and antibiotics, were implemented.

5. Results

5.1. Procedure results

The results are shown in Table 1. ESD was performed resoundingly on all patients. The success rate of the ADM membrane graft implantation was 100% (11/11).

5.2. Clinical outcomes

Table 1 showed the clinical outcomes. All patients safely received ESD and endoscopic transplantation of ADM without any severe adverse events, for instance, obvious immediate bleeding or perforation. The longest operation time of mucosal transplantation was 150 min, the shortest was 60min, and the median time was 84 min. It took an average of 183.6 min (range 135–270) to complete the entire procedure. As for tumor invasion depth confirmed by pathology, there were 2 sm1 lesions (slightly invasive carcinoma into the submucosa with a depth less than 200 μm), 1 sm2 (moderately invasive carcinoma into the submucosa with a depth of 200um-400um), 2 m1 lesion (intramucosal invasive carcinoma limited to epithelial layer) and 1 m2 lesions (intramucosal invasive carcinoma limited to mucous lamina propria), and 1 m3 lesion (intramucosal invasive carcinoma limited to mucous membrane). As an ESD-related adverse event with high probability of occurrence, esophageal stricture is still an urgent problem to be solved. Lesion location, longitudinal diameter more than 40 mm, and circumferential extension >3/4 are considered to be important factors for predicting the occurrence of post-ESD stenosis [3]. After ESD operation for esophageal tumors, ADM was transplanted to the local lesions and fixed with esophageal mulching stents to prevent the formation of

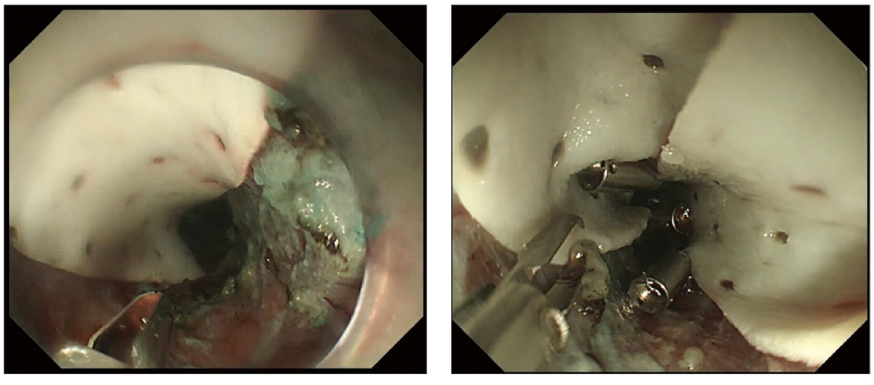

Fig. 1. Placement of acellular dermal matrix when the width of the mucosal defect > 4 cm.

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Table 1
Clinical outcomes and follow-up for 7 patients with early esophageal cancer after 3/4-circumferential ESD.

Case no	Age (y/sex)	Lesion location	Longitudinal diameter of specimen (mm)	Operation time of mucosal transplantation (min)	Histological depth	Stricture	Time of stricture (day)	No. Of EBD	No. Of mucosal patches/day	Time of the first postoperative endoscopic examination (month)	Endoscopic view	Follow-up (month)
Case 1	71/Male	Upper-Middle	65	60	M1	(+)	42	9	3	1.5	proliferating squamous epithelium with a few interstitial lymphocytes and neutrophils infiltrating	12
Case 2	59/Male	Upper-Middle	55	150	SM1	(+)	140	2	4	10	proliferating squamous epithelium with a few interstitial lymphocytes and neutrophils infiltrating	10
Case 3	65/Female	Middle	38	98	M3	(−)	/	/	2	3	proliferating squamous epithelium with a few interstitial lymphocytes and neutrophils infiltrating	7
Case 4	71/Male	Lower	50	80	M2	(−)	/	/	2	2	proliferating squamous epithelium with a few interstitial lymphocytes and neutrophils infiltrating	6
Case 5	65/Male	Middle	50	84	SM2	(+)	79	2	6	4	Inflammatory necrosis and granulation tissue hyperplasia, lymphocytes, neutrophils infiltration	5
Case 6	73/Female	Upper-Middle	90	100	SM1	(−)	/	/	3	1	proliferating squamous epithelium with a few interstitial lymphocytes and neutrophils infiltrating	1
Case 7	73/Female	Upper-Middle	60	61	M1	(−)	/	/	3	4	proliferation of free squamous epithelium	4

postoperative esophageal stenosis (Fig. 2). The average longitudinal diameter of the resected specimens was 58.3 mm (range 38–90 mm). Two to six ADM patches, in the light of the size of ulcer surface, were implanted into the mucosal defect. Three of seven patients developed esophageal stenosis postoperatively at a mean of 87 days (range 42–140 days). The median number of postoperative endoscopic balloon dilatation (EBD) in patients with stenosis was 2 (range 2–9). Postoperative reexamination of endoscopy revealed that, except for one patient with inflammatory necrosis covering, granulation tissue hyperplasia and more infiltration of lymphocytes and neutrophils, all the other patients had proliferative squamous epithelial cells accompanied by a few chronic inflammatory cell infiltration. And there were no deaths during the median follow-up period of 6 months (range 1–12 months).

5.3. Endoscopic examination

Fig. 1 showed healing of the ulcer and progression of the stenosis after ESD observed under the endoscope. Four weeks after, the size of ulcer became significantly smaller with development white scar tissue.No cases of serious stenosis showed in the ADM treated group, except for only 1 case the gastroscope meeting resistance to crossing the stricture.

6. Discussion

In this study, we used ADM to prevent the formation of postoperative esophageal stenosis. It was shown in previous studies that patients with circumferential defects were more likely to suffer from severe stricture than those with local defects, and this result was also confirmed in the present study. Two EGC patients underwent whole circumference endoscopic dissection, all of which developed postoperative stricture at 42 days and 142 days, respectively. Nevertheless, favorable clinical outcomes arose in the non-whole circumference group, in which postoperative stenosis only occurred in one patient of the remaining five cases during a median follow-up period of 5 months (range 1–7 months). In past studies, clinicians chose insertion of temporary stent and injection of local steroid to prevent esophageal stenosis after ESD. However, these methods have their own disadvantages and perform not satisfactory. It has been reported that patients need as many as 32 times of dilation sessions after circumfernatial ESD [20]. In the study of Sato et al. even using steroids after dilatation, an average of 13.8 dilatations are still required in patients with circumferential esophageal ESD [30]. Our results proved that though autologous esophageal mucosa transplantation had little effect on reducing the frequency of stenosis formation, it showed significant effect on reducing the mean number of dilatation sessions required. Our results demonstrated that ADM transplantation combined with esophageal stent can significantly reduce the formation of esophageal stricture, which requires dilatation in almost one in ten patients.

In 2017, Ye et al. transplanted tissue-engineered acellular dermal matrix sheets to prevent post-ESD stricture in porcine model. Acellular grafts are regenerated with great properties, such as the ability to attract or recruit host esophageal epithelial and smooth muscle cells into the graft, without which the tissue building process will never be completed [31]. Cell-free grafts are involved in regulating the process of tissue integration, including vascularization, inhibition of scar formation, wound contraction, early tissue remodeling and reduction of inflammation [32,33].

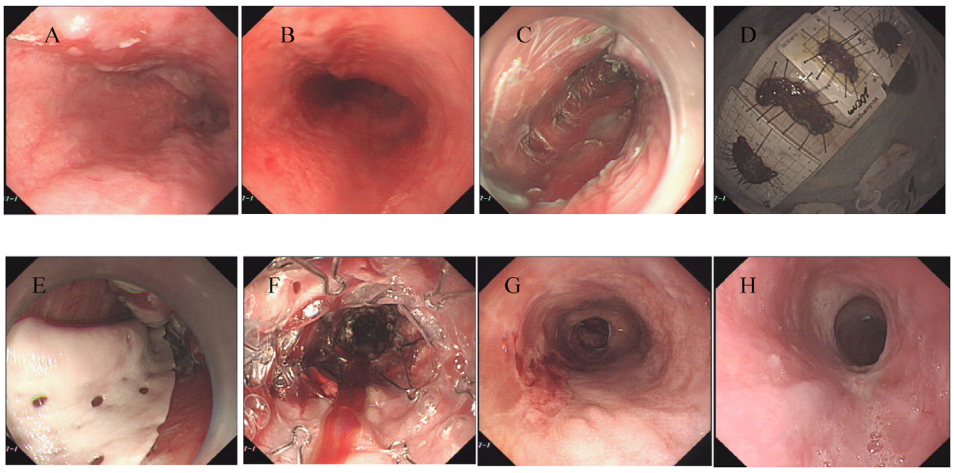

Fig. 2. Procedure of acellularized dermis matrix transplantation plus fully covered metal stent. A-B, Multiple esophageal mucosal dysplasia. C-D, ESD for esophageal mucosal lesions. E, ADM transplantation. F, Esophageal mulching stent implantation compressed transplanted mucosa. G, The stent was removed 2 week after the procedure. H, 1 month after ESD operation, no significant stenosis was observed.

7. Conclusion

In this study, ADM grafts were first time implanted into the digestive tract and fixed with metal clips. The healing of ulcer benefits from the favorable environment created by the ADM. Our study demonstrated that insertion of ADM graft has the ability to significantly reduce the occurrence rate of esophageal stenosis after after semi-circumferential ESD. We suggest that mechanisms such as early formation of epithelialization, minimized inflammatory response, and rapid tissue remodeling may explain the reason why ADM implantation promotes ulcer healing.

In conclusion, we hold opinion that efficacy of insertion autologous mucosal grafts in reducing the formation of stenosis after circumferential ESD is considerable and worthy of expectation.

Declaration of competing interest

The authors declare that they have no conflict interests.

Acknowledgements

This work was supported in part by the Key technology research and development program in Zhejiang Province (2019C03040), Medical Science and Technology Project of Zhejiang Province (2021PY083), Program of Taizhou Science and Technology Grant (20ywb29), Open Project Program of Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumor of Zhejiang Province (21SZDSYS01, 21SZDSYS09) and the Major Research Program of Taizhou Enze Medical Center Grant (19EZZDA2).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2021.10.002.

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