

Efficacy and histopathological esophageal wall damage of biodegradable esophageal stents for treatment of severe refractory esophageal anastomotic stricture in a child with long gap esophageal atresia

Yuichi Okata · Chieko Hisamatsu · Yuko Bitoh · Akiko Yokoi · Eiji Nishijima ·
Kosaku Maeda · Makiko Yoshida · Tsukasa Ishida · Takeshi Azuma ·
Hiromu Kutsumi

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Abstract A case in which a self-expandable biodegradable (BD) esophageal stent was used for a refractory esophageal anastomotic stricture (EAS) in a 5-year-old female is presented. The patient underwent closure of a tracheoesophageal fistula and gastrostomy in the neonatal period. Esophagoesophagostomy was performed at 18 months of age after a multistaged extrathoracic esophageal elongation procedure. The patient developed refractory EAS and required repeated esophageal balloon dilation. Four sessions of esophageal BD stenting were performed from the age of 5–8 years. Each BD stenting allowed her to eat chopped food, but the anastomotic stricture recurred 4–7 months after the procedure. No major complications were observed, though transient chest pain and dysphagia were observed after each stenting. Finally, at 8 years of age, EAS resection and esophagoesophageal anastomosis were performed. The resected specimens showed thickened scar formation at the EAS lesion, while the degree of esophageal wall damage, both at the proximal

and distal ends of the stricture, was slight. To the best of our knowledge, this is the first case report of this kind of treatment and assessment of damage to the esophageal wall microscopically. The advantages and problems of the use of BD stents in children are discussed.

Keywords Esophageal atresia · Refractory · Anastomotic stricture · Stent · Biodegradable

Introduction

Refractory esophageal anastomotic strictures (EASs) after repair of esophageal atresia (EA) often require frequent dilation [1]. However, repeated esophageal dilation increases the risk of complications such as esophageal perforation, and may lead to psychological problems due to the need for repeated procedures under anesthesia, especially in children.

Recently, some studies have reported the efficacy of biodegradable (BD) stents for treating refractory benign esophageal strictures in adult patients [2, 3]. However, the efficacy and safety of BD esophageal stents in pediatric patients are unknown.

The case of a child with refractory EAS treated by a self-expandable BD esophageal stent who needed frequent esophageal balloon dilation after surgical repair of a long gap EA is reported.

Case report

A female patient was born at 32 weeks gestation with a birth weight of 1,476 g. She was diagnosed with esophageal atresia on the day of birth and underwent gastrostomy

Y. Okata (✉) · C. Hisamatsu · E. Nishijima · K. Maeda
Division of Pediatric Surgery, Department of Surgery, Kobe
University Graduate School of Medicine, 7-5-2 Kusunoki-cho,
Chuo-ku, Kobe 650-0017, Japan
e-mail: yuichi.okata@gmail.com

Y. Okata · Y. Bitoh · A. Yokoi · E. Nishijima · K. Maeda
Department of Pediatric Surgery, Kobe Children's Hospital,
Kobe, Japan

M. Yoshida
Department of Pathology, Kobe Children's Hospital, Kobe,
Japan

T. Ishida · T. Azuma · H. Kutsumi
Division of Gastroenterology, Department of Internal Medicine,
Kobe University Graduate School of Medicine, Kobe, Japan

on day 1 after birth. At the age of 15 days, tracheo-esophageal fistula closure and esophagostomy were performed, because she was diagnosed with long gap EA (Gross's classification type B). The gap was three vertebral lengths long. Subsequently, she underwent multistaged extrathoracic esophageal elongation procedures [4, 5] at 6, 8, and 12 months of age. At the age of 18 months, esophagoesophagostomy was performed via a thoracotomy. After the operation, anastomotic leakage and frequent vomiting caused by severe gastroesophageal reflux occurred. Thereafter, she underwent an anti-reflux operation (Nissen's fundoplication) at the age of 20 months. At 23 months of age, esophagography revealed an EAS, for which esophageal endoscopic balloon dilation was performed. However, she developed refractory EAS resistant to frequent attempts at balloon dilation combined with intravenous and/or oral administration of steroids. She also had magnetic compression revision anastomosis for the EAS [6] at 3 years of age, although even this procedure could not relieve the EAS. Therefore, she needed frequent balloon dilations. At 4 years of age, she suffered esophageal perforation and mediastinitis due to esophageal balloon dilation, both of which were treated conservatively.

She repeatedly underwent progressive esophageal balloon dilation once or twice a month until the age of 5 years, when she was referred to our hospital for further therapy. With the approval of the Ethics Committee of Kobe University Graduate School of Medicine and after informed consent was obtained from the patient's parents, esophageal stenting with an 18-mm-diameter and 40-mm-long BD stent (Ella-CS, Hradec Kralove, Czech Republic) was performed (Fig. 1). The stent diameter was chosen to fit the upper and lower lumens of the esophageal strictures, and the stent length was made slightly longer to avoid stent dislocation. Under general anesthesia, after balloon dilation of the EAS, the BD stent was placed. The stent insertion procedure was performed easily and safely. Immediately after awakening from general anesthesia, severe retrosternal pain, nausea, and dysphagia occurred. The intensity of the thoraco-abdominal pain was so severe for the first few days (Wong-Baker scale 4–5) that she required continuous intravenous infusion of analgesic agents (fentanyl 0.5 $\mu\text{g}/\text{kg}/\text{h}$). Although these symptoms continued for a week, they gradually improved. After the pain and nausea improved, she was able to take chopped food orally without any symptoms. Three months later, dysphagia recurred.

Fig. 1 Endoscopic findings before stent insertion (40-mm-long) show a complicated anastomotic stricture (*arrow*) (a). Images immediately after esophageal stent insertion (b). Contrast study after stent placement (c)

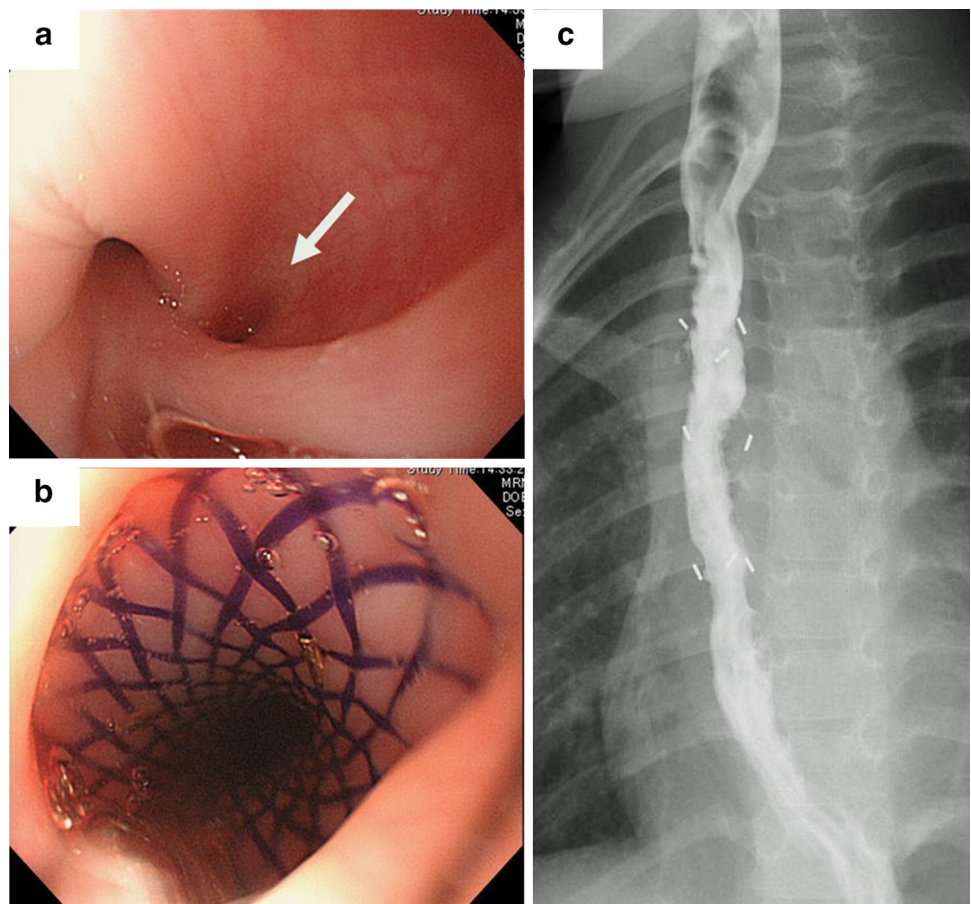


Fig. 2 Endoscopic findings 3 months after insertion of a 40-mm-long BD stent. Most of the stent has degraded and in-growth of granulation tissue through the stent mesh is observed (**a, b**). The anastomotic stricture site remains patent, (**a**) but a second stricture formation is seen at the distal end of the stent (**b**)

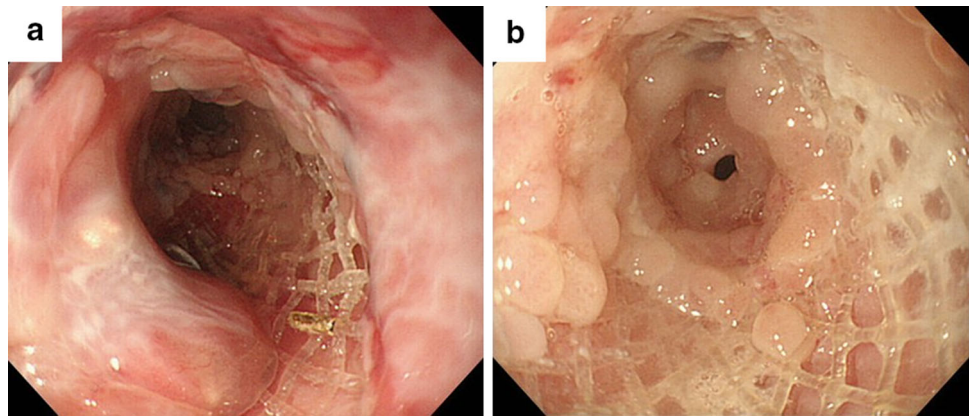
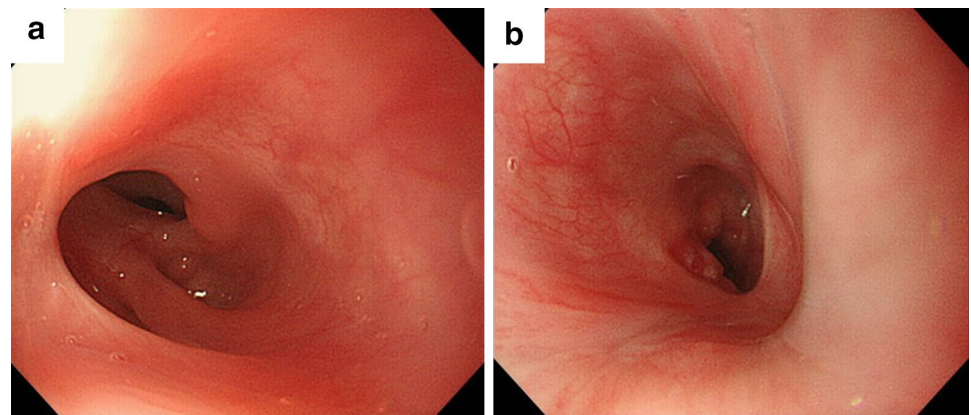


Fig. 3 Endoscopic findings 5 months after stent insertion. The anastomotic stricture has recurred, (**a**) although the stricture at the distal end of the stent is seen to have improved (**b**). The in-growth of granulation tissue through the stent mesh has diminished spontaneously (**a, b**)



Endoscopy performed at this time revealed a second stricture at the distal end of the stent, which required endoscopic balloon dilation and in-growth of granulation tissue through the stent mesh (Fig. 2). While the second stricture showed a tendency to improve, the original anastomotic stricture recurred 5 months after stent placement, although the previously observed in-growth of granulation tissue diminished spontaneously (Fig. 3).

Both the patient and her parents desired reinsertion of the BD stent to enable her to take meals orally. Therefore, a second stenting procedure was performed. The second stent was selected to dilate both the original EAS and the second stricture that was induced by the first stenting procedure and to fit the stent to the long axis of the esophagus. Postoperative thoraco-abdominal pain and vomiting were more severe than after the first stent, and she required strict pain management with an analgesic agent for a few days. Once again, the symptoms gradually improved, and she resumed eating. Five months later, a third slight stricture developed at the distal end of the second stent, as seen by esophagography, although it did not require balloon dilation. Seven months later, dysphagia recurred again, and endoscopy revealed recurrence of the original EAS, while the second and third strictures improved spontaneously. We recommended an operation for re-anastomosis of the

esophagus to the patient and her parents, but we could not obtain consent from her parents. They instead preferred repeat BD stenting, because the BD stent improved oral intake for several months with less invasion.

Hence, a third BD stent was inserted 18 months after the first stent. This time, a slightly smaller and shorter stent with a diameter of 15 mm and a length of 40 mm was used because we hypothesized that this may prevent further stricture formation at the distal end of the stent; we expected post-stenting symptoms to be decreased since the stent-end side would be located in a straight line with the esophagus, thereby decreasing the stimulus resulting from stent extension. In fact, following this procedure, post-stenting symptoms were not severe, and the patient needed a single-dose of an analgesic agent (flurbiprofen 1 mg/kg) postoperatively. However, another stricture formed, this time at the proximal end of the stent, which required balloon dilation 5 months after the third stent placement.

Thereafter, a fourth BD stenting was performed. This stent was of the same length (40 mm) but with a stent body of a smaller diameter (14 mm) and a flare (16 mm) at the oral end to avoid stricture formation at the proximal side of the stent. Post-stenting symptoms were slight, and she did not require any analgesic agents, and no further stricture formation was observed at either end of the stent, although

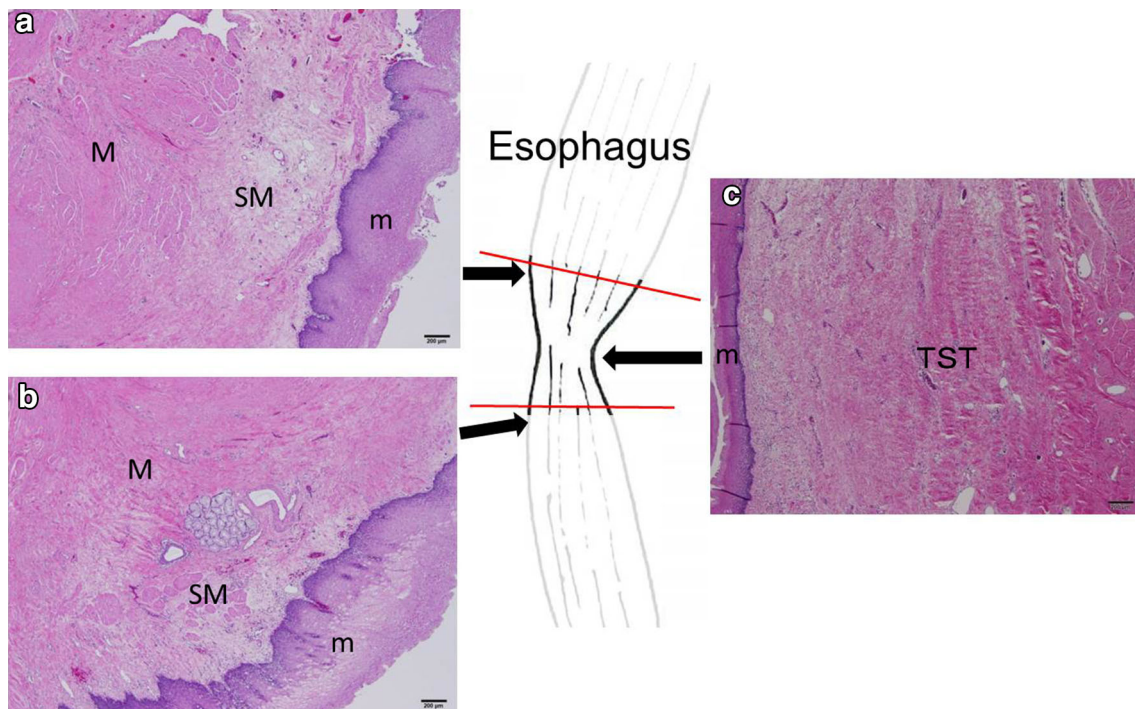


Fig. 4 There is no evidence of residual stent material on both macro and microscopic examinations. Both the upper and lower ends of the specimen have normal mucosal (m) and submucosal layers (SM), although irregular arrangement of the muscle layers (M) is observed

(a upper segment of the resected esophagus, b lower segment of the resected esophagus). The anastomotic stricture lesion is composed of thickened scar tissue (TST) without any component of normal esophageal wall, but with a thin mucosal layer (c)

the anastomotic stricture recurred 9 months after the fourth stent placement.

Finally, she underwent resection of the anastomotic stricture and end-to-end anastomosis of the esophagus via a right thoracotomy at the age of 8 years. Intraoperatively, there were severe adhesions around the anastomotic stricture lesion, and the esophagus was kinked backwards, although the adhesions around the upper and lower parts of the esophagus where the BD stents were placed were slight, suggesting little effect of the stent on the adhesions. After the operation, a minor anastomotic leakage was observed, which, however, healed conservatively, and she became able to eat standard foods.

Pathological evaluation of the resected specimen revealed that the anastomotic stricture lesion was composed of thickened scar tissue without any component of normal esophageal wall, while both the proximal and distal ends of the stricture were almost normal (Fig. 4).

Discussion

Various stenting devices, such as fully or partially covered self-expanding metal stents (SEMSs) and covered self-expanding plastic stents (SEPSs), are available for refractory benign esophageal strictures in adult patients [7, 8].

Currently, the use of SEPSs in patients with benign esophageal strictures has been proposed as an alternative to SEMSs, because SEPSs have shown the same degree of relief of dysphagia; the lower major complication rate could reduce reactive tissue hyperplasia, and they could be removed more easily than SEMSs [7–9]. In pediatric patients, the use of SEMSs or SEPSs is limited, because the degree of damage to the esophageal wall following stenting is unclear [10, 11], and esophageal stents have been fundamentally adapted only for the treatment of stenosis secondary to malignant lesions. Thus, their long-term effects on the human body are unknown.

The BD stent which was used in the present case is made of the same material as polydioxanone absorbable surgical sutures. Degradation occurs 11–12 weeks after insertion by random hydrolysis of its molecule ester bonds and is accelerated by low pH [11]. Thus, we hypothesized that this BD stent may be preferable for use in growing children since it does not require removal, and it might decrease the re-intervention rate for complications such as stent migration.

Recent studies addressing the efficacy of BD stents in patients with refractory benign esophageal anastomotic strictures have shown a dysphagia-free success rate of 33 or 45 %. In terms of complications, the stent migration rates were variously 22.2 and 9.5 %, and post-stenting pain

rates were 11.1 and 14.3 % [2, 3]. These data showed results equal to or greater than those of SEPSs [9]. Van Boeckel and colleagues' report also showed that the success rate and complication rate of BD stents were equal to those of SEPSs, and that the rate of re-interventions after BD stenting was lower than that of SEPSs [12].

Since reports regarding the use of BD stents for esophageal strictures in children are extremely limited [13], the efficacy and problems of the use of this stent in pediatric patients are unknown.

In the present case, four sessions of BD stenting were able to prolong the intervals between esophageal balloon dilation, extending the symptom-free period and temporarily improving oral intake without major complications such as perforation. We speculated that the reason for stricture recurrence after each BD stenting could be related to severe and tight scar formation at the site of the initial esophageal anastomotic stricture.

The problems of using BD stents in children include post-stenting symptoms and further stricture formation at the proximal or distal end of each stent. It is difficult for children to handle symptoms such as chest pain and discomfort; these should be avoided in children. The present patient required intravenous analgesic therapy during the early post-stenting period following the first and second stent insertions. Based on these experiences, we used smaller or shorter stents for the third and fourth attempts. These stents could palliate her symptoms, suggesting that the severity of post-stenting symptoms could have been associated with the longer stent length and mismatch in luminal size between the esophagus and the first and second stents.

In terms of the new stricture formation that occurred temporarily at the proximal and distal ends of the stent, we speculate that these strictures may have been induced by continuous mechanical stimulation of the esophageal wall by the stent. Hence, diminution of the mismatch in luminal size and axis direction between the esophagus and the stent may prevent these stricture formations.

Regarding the degree of esophageal wall damage by the BD stent, there is only one previous case report with histological findings of a resected esophagus after BD stenting for corrosive esophageal strictures [14]. Although replacement fibrosis in the mucosal layer, ulceration of the mucosa, and granulomas were documented microscopically in that report, it was unclear whether these changes were caused by the BD stent or were the result of corrosive esophagitis. In the present patient, the degree of influence of multiple BD stenting on the esophageal wall could be assessed by observation of the resected esophageal specimen. Although tight fibrosis was present at the anastomotic portion, there were almost no microscopic findings of mechanical and chemical damage induced by the BD stent

in the esophageal wall. Since the stent degrades within 3 months, the damage or stimulation by the BD stent may be transient and may not be detected pathologically.

Another concern is the possible combination of the BD stent with anti-fibroblastic agents such as mitomycin C, sirolimus, and steroids. As possible approaches, there are topical applications of anti-fibroblastic agents at the time of BD stenting after balloon dilation and oral/intravenous steroids. When we take into account esophageal wall injury by esophageal balloon dilation before stenting, as we previously reported [15], basic fibroblast growth factor (bFGF) could be an ideal anti-scarring agent to use in combination with the BD stent. In a recent study, a rapamycin-eluting metal stent led to a longer retention period in a canine esophageal stricture model. Therefore, future work should include examination of drug-eluting BD stents.

Conclusion

In the present case, the advantages of BD stenting were prolongation of the interval between esophageal balloon dilations, extension of the symptom-free period, and temporary improvement of oral intake without major complications. However, BD stenting may not be a definitive treatment for esophageal strictures with tight scar formation. When using the BD stent in children, determination of the proper diameter and length of the BD stent and pain control after stenting may be difficult.

Disclosures

Conflict of Interest: Yuichi Okata, Chieko Hisamatsu, Yuko Bitoh, Akiko Yokoi, Eiji Nishijima, Makiko Yoshida, Tsukasa Ishida, Takeshi Azuma, Kosaku Maeda, and Hiromu Kutusmi declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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