Patch Esophagoplasty: Esophageal Reconstruction Using Biologic Scaffolds

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Background. Standard techniques for surgical reconstruction of the esophagus remain suboptimal. Primary closure of diseased or injured esophagus has been associated with high morbidity, primarily due to leak and stricture, and synthetic materials are contraindicated due to the high risk of erosion and infection. Degradable bioscaffolds composed of extracellular matrix (ECM) have recently shown promising results in both preclinical and clinical settings to prevent stricture after extended endoscopic mucosal resection. We propose a novel surgical technique that utilizes an ECM scaffold as a reconstructive patch to augment the esophageal diameter during primary repair.

Methods. Four patients requiring esophageal reconstruction underwent a patch esophagoplasty using an ECM scaffold composed of porcine urinary bladder ECM. The full thickness wall of the esophagus was replaced with an ECM patch that was sutured to the edges of the remaining esophagus, similar to the patch angioplasty performed in vascular procedures.

Results. All patients had a favorable clinical outcome with immediate recovery from the procedure and reinstated oral intake after 7 days. One patient had a micro leak at day 5 that closed spontaneously 2 days after drainage. Follow-up studies including barium swallow and esophagogastrroduodenoscopy (EGD) showed adequate esophageal emptying through the surgical segment in all patients. The EGD showed complete mucosal remodeling at 2 months, with approximately 20% area contraction at the patch level. The area of the defect was indistinguishable from surrounding healthy tissue. Biopsy of the patch area showed normal squamous epithelium. One of the patients had a separate intrathoracic stricture that required further surgery. Clinical outcomes were otherwise favorable in all cases.

Conclusions. An alternative for the treatment of esophageal stenosis is presented which uses a biological scaffold and an innovative surgical procedure. Additional work, including prospective studies and long-term follow-up, is required to fully evaluate the potential of this bioscaffold-based regenerative medicine approach for esophageal reconstruction.

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Surgical reconstruction of the esophagus after stricture formation or esophageal damage remains a challenge. Current strategies often include multiple complex procedures to restore partial organ functionality and without exception are associated with morbidity and complication rates as high as 30% to 40% [1–3]. In addition, the need for postsurgical dilations in more than 50% of the cases [4] contributes to a substantial decrease in quality of life [4, 5].

Benign strictures are a common finding after esophageal surgery, and caustic or peptic injuries. Although endoscopic therapies are the first choice of treatment and are successful in the vast majority of cases, refractory strictures are not rare and often need surgical correction [6]. The alternatives for esophageal reconstruction after failed primary surgeries are scarce and usually involve a new conduit interposition or the use of a pedicled tissue flap to restore the remaining esophagus [7–9]. In fact, extended esophageal damage often requires radical esophagectomy even for benign conditions due to the lack of effective treatment options [10]. Degradable extracellular matrix (ECM) scaffolds have recently shown promising results in both preclinical and clinical settings [11, 12]. Endoluminal deployment of the scaffolds has recently been shown to prevent stricture after extended endomucosal resection for adenocarcinoma allowing for esophageal preservation in patients who would have otherwise undergone an esophagectomy. In preclinical studies, large full thickness esophageal defects have been successfully reconstructed. In other tubular organs such as the urethra, ECM patches have been utilized successfully in patients to reconstruct defects and to augment tissue. The first 4 cases of a patch esophagoplasty in which biologic scaffolds were used to...
augment and restore the damaged esophageal tissue are reported herein.

**Patients and Methods**

Due to the retrospective nature of the study, the Institutional Review Board waived specific informed consent for publication if confidentiality of patients was maintained. All patients signed individual informed consents prior to the surgery.

**Patient 1**

A 58-year-old woman was referred after a laparoscopic Nissen with hiatal mesh reinforcement (polypropylene) who had a poor outcome over the course of 2 years with progressive dysphagia and severe weight loss. Barium swallow showed a linear stenosis in the distal esophagus with signs of mesh intrusion into the lumen. Mesh intrusion was corroborated by esophagogastroduodenoscopy (EGD). At reoperation, a massive contained abscess in the mediastinum was found around the mesh that had migrated into the chest. During the take down, and after mesh extraction, a large esophageal defect of 5 cm was present with the lower third of the esophagus being disrupted and devitalized (Fig 1).

**Patient 2**

A 28-year-old man underwent cervical esophageal exclusion due to esophageal perforation, which was followed by a severe mediastinitis that required 23 days of respiratory assistance and 60 days in the intensive care unit. After recovery of the acute syndrome, the patient was referred for closure of the lateral esophagostomy. During the reconstruction, a stricture was noticed at the center of the loop leaving a very narrow lumen for primary repair.

**Patient 3**

An 8-year-old boy presented with history of caustic ingestion at the age of 3. He had received repeated dilations until a perforation with subsequent mediastinitis occurred. At that time he had a bypass done with a coloplasty that developed ischemia and subsequent fibrosis that led to 2 strictures; 1 stricture at the anastomosis level and 1 intrathoracic. He underwent repeated dilations and stent placing without positive results and was referred for surgical repair. The cervical stricture was approached initially as it appeared short but this became more severe during repeated dilations.

**Patient 4**

A 57-year-old male had undergone an esophagectomy for adenocarcinoma of the esophagus. He was reconstructed with a gastroplasty and a cervical anastomosis that leaked and led to a postoperative stricture. The stricture was treated conservatively with repeated endoscopic dilations and a cervical stent placement. The outcome of those dilations was consistent recurrence of the stricture 5 days after each dilation or stent removal. After 10 dilations over a 4-month period, surgery was performed.

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**Fig 1.** A 58-year-old patient with a synthetic mesh inclusion after a hiatal hernia repair. (A) Barium swallow showing the mesh inclusion and lack of esophageal transit. (B) Damaged esophagus after mesh take-down at the gastroesophageal junction level. (C) Patch esophagoplasty with urinary bladder matrix-extracellular matrix to augment esophageal tissue and prevent stricture after closure. (EW = esophageal wall; ED = esophageal defect; ES = extracellular matrix scaffold.)
Surgical Procedure

All surgical procedures were performed at Favaloro Foundation University Hospital in Buenos Aires, Argentina. A patch esophagoplasty with urinary bladder matrix-ECM (MatriStem, ACell Inc, Columbia, MD) was performed in all cases to augment the esophageal tissue and enlarge luminal diameter following the same concept of a carotid patch angioplasty. The patch (US Food and Drug Administration-approved and commercially available) consists of 8 layers of porcine urinary bladder matrix that are lyophilized and have an intact basement membrane layer considered to be the luminal side. In patient 1, the defect was covered with a 5 × 3 cm patch that was sutured to the lower third of the esophagus with interrupted stitches through a midline laparotomy. A Nissen fundoplication was completed on top. In patient 2, a 4 × 2 cm patch was used with interrupted stitches and the patch was covered with the overlapping sternocleidomastoid through a lateral cervicotomy. In patient 3, accessing through a lateral cervicotomy the esophagus was split longitudinally at the cervical stricture level that was only 2-cm away from the pharynx, and then a 5 × 3 cm esophagoplasty was performed with running sutures and the remaining cervical fascia was closed on top. In patient 4, accessing through a lateral cervicotomy a stricturoplasty was performed under endoscopic guidance and the esophagus was opened longitudinally through the stricture and up to 2 cm over the gastric conduit. A 5 × 2 opening was achieved and a 5 × 2 ECM patch was implanted to restore and augment the lateral wall of the esophagus. No muscle or skin flaps were utilized. Proton pump inhibitors twice a day were used in all cases during the first postoperative month. In all cases, the basement membrane layer of the patch was facing to the lumen of the esophagus. Mean duration of the procedures was 94 minutes ± 45 minutes with a blood loss less than 100 mL.

Results

Patient 1

Patient 1 had an uneventful clinical outcome with rapid postoperative recovery. Oral intake was reinstated at day 5 after a barium swallow showed no leaks and normal emptying of the esophagus. She was discharged at day 6. At 4 months follow-up, an EGD showed normal lumen and complete epithelialization, and a biopsy taken at the patch level showed normal squamous epithelium. At 16-months follow-up the patient continues to gain weight, and went back to a normal diet (Fig 2).

Patient 2

Patient 2 had a favorable postoperative outcome and was discharged at day 2 with a wound drain in place. Because the patient had a jejunostomy from the previous surgery, that route was used to feed him until oral intake was reinstated. At day 5, a minor leak with less than 3 mL in volume and no signs of infection was detected and the cervical wound opened partially to allow complete drainage. Three days later oral intake was progressively reinstated. Barium swallow at 21 days showed no narrowing of the lumen at the cervical level and normal esophageal emptying. At 2-months follow-up, EGD showed complete epithelialization and the area where the patch was implanted showed clear ingrowth of blood vessels. At 12-months follow-up the patient has resumed a complete normal diet and is free of dysphagia.

Patient 3

Patient 3 had an uneventful recovery from the surgery and was discharged at day 2 with feeding through the gastrostomy that he previously had. Oral intake was reinstated at day 7. No leaks were observed and the drain was removed that same day. At 1 month, the repaired area could clearly be seen in the EGD with a pliable remodeling patch. Barium swallow showed correction of

Fig 2. Follow-up after patch esophagoplasty repair. (A) Barium swallow at 5 days showing no leaks and clear esophageal transit. (B) Biopsy of the patched area after remodeling showing normal squamous epithelium. (Hematoxylin eosin staining, magnification 4×.)
the cervical stricture and narrowing in the intrathoracic portion of the conduit. At 1 year, the cervical esophagus had a normal appearance and repeated dilations were being performed on the distal stricture. Cervical luminal diameter was maintained and no tearing at that level was observed after dilations. The distal stricture is refractory to endoscopic treatment and the patient is in program for conduit replacement. Although the second stricture was too long for this type of approach, the aim of treating the first stricture was to gain esophageal length below the pharynx to implant the future conduit (Fig 3).

Patient 4
Patient 4 had a favorable clinical outcome with no leaks and immediate sensation of relief. Oral intake was reinstated after 7 days with clear passage of liquids and semisolids. During the first 4 months he required 4 dilations to calibrate the diameter. Upon interrogation, his sensation of dysphagia from 1 to 10, setting as a subjective value of 1 the day before surgery, improved over 50% before dilations and up to 90% after dilations compared with his status prior to surgery. At 6 months he resumed a normal diet and no further dilations were required. As opposed to preoperative dilations, after the esophagoplasty the tissue was more pliable and tear always occurred in the posterior wall where the scar was in the native esophagus (Fig 4).

Comment
The first 4 patients with full thickness esophageal replacements using biologic scaffolds are presented and a novel surgical procedure is described. All patients had a severely diseased esophagus with conditions that would have resulted in esophageal resection or morbid surgical procedures under the standard of care. With the ECM esophagoplasty procedure, all patients were able to save their esophagus and recover functionality without major complications.

Esophageal stricture remains a challenge for the esophageal surgeon when endoscopic therapies have failed. Very often, patients are treated endlessly with dilations and interventional procedures because surgical solutions are difficult and involve morbid procedures, and results are usually suboptimal. The most common surgical procedures for an esophagoplasty when tissue augmentation is needed are a pedicled muscle flap or a jejunum interposition. Necrosis of the graft or infection of the donor area are common findings that significantly alter a patient's quality of life. The patch esophagoplasty using an off the shelf ECM scaffold avoids the use of a flap with no major complications and can serve as a useful tool for recurrent strictures. Patch esophagoplasty may be indicated when endoscopic treatments begin failing, without the need to wait until surgery becomes only a rescue procedure. Synthetic devices such as composite meshes are not an alternative for tissue augmentation in the esophagus because of their tendency to get infected and rejected. The ECM scaffolds derived from decellularized tissues have been widely used to promote site-appropriate tissue remodeling in a variety of applications including vascular [13–15], esophageal [8, 16–18], tracheal [19, 20], cardiac [21, 22], and muscular tissues [23, 24] among others. These ECM scaffolds consist of the structural and functional molecules secreted by the local...
cells of each source tissue, and therefore the specific composition of ECM scaffolds varies depending on the tissue from which the ECM is harvested [25]. The ECM scaffolds are composed of more than 90% collagen, the majority of which is collagen type I, with lesser amounts of collagen types III, IV, V, VI, and VII [26, 27] In addition, these naturally occurring acellular scaffolds contain growth factors such as vascular endothelial growth factor [28], fibroblast growth factor, and others [29]. Upon implantation, ECM scaffolds degrade quickly, releasing matricryptic peptides that contribute to the remodeling process [30, 31] by promoting angiogenesis [32, 33], stem cell recruitment and proliferation [34, 35], and modulating the immune response [36–38]. The ECM has been shown to be instrumental in tissue development [39, 40] and to be responsive to changes in the microenvironmental niche condition. Mechanical properties of ECM scaffolds has also been well characterized, particularly for the esophagus, where it has been shown that as remodeling occurs the strength and compliance tend to mimic those of the native organ [8]. In summary, ECM scaffolds have a complex composition with a variety of diverse bioactive molecules that support the cellular processes necessary for optimal tissue function and repair.

Particularly for the esophagus, animal models have had promising results [8, 16–18]. Early reports showed that extracellular matrix derived biomaterials can be used to repair small patch defects of about 40% to 50% of the circumference encompassing the full thickness of the esophagus [32], reinforce anastomoses [16], or restore full circumferential repairs when at least 30% of abluminal muscle was left in contact with the scaffold. In all cases, full thickness histology has shown complete remodeling of the scaffolds replaced with native organized tissue and complete epithelialization. Moreover, in the first clinical report of these applications, it has shown that stricture can be prevented after extended circumferential mucosal resection in 5 patients [18]. The bridge size threshold to reconstruct a hollow organ with ECM scaffolds has not been defined yet, but based on preclinical studies of cell ingrowth, repair of a defect with a maximum width of approximately 3 cm can be achieved using ECM without the need of adding a cellular component [41].

Limitations of the present study include the heterogeneity of the clinical cases that do not allow for description of standardized operative procedure. This report includes only 4 patients and therefore must be considered as pilot data. Longer term follow-up is required as severe structures can recur even after some years of initial dilation but the significant improvement observed herein compared with the preoperative condition is encouraging.

In conclusion, an alternative for the treatment of esophageal stenosis is presented which uses a degradable biologic scaffold and an innovative surgical procedure. Although most of the patients are alleviated by endoscopic interventions, the described patch esophagoplasty alternative may provide further relief with increased safety in refractory cases. The description is limited to 4 patients but outcomes are encouraging and the results are consistent with those observed in preclinical studies. Additional work, including prospective studies and long-term follow-up is required to fully evaluate the potential of this bioscaffold-based regenerative medicine approach for esophageal reconstruction.

References

INVITED COMMENTARY

The usual response to tissue injury or loss is an inflammatory reaction that leads to variable degrees of collagen deposition and scar formation. While this default response replaces missing tissues and maintains structural integrity it often impairs organ function. Tissue injury in some organs such as the epidermis, gastrointestinal epithelium, bone marrow, and liver triggers a substantial increase in health care costs. The esophagus is a good example of such organs where intractable anastomotic strictures after esophageal reconstruction or esophageal tissue loss or stenosis that follows spontaneous or iatrogenic esophageal disruption may lead to significant morbidity, including dysphagia and aspiration.

Recent advances in cell biology, bioengineering, and regenerative medicine led to the development of...