Ureteral reconstruction with decellularized small intestinal submucosa matrix for ureteral stricture: A preliminary report of two cases

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Abstract
Objective: To determine the feasibility of decellularized small intestinal submucosa (SIS) matrix in repairing ureteral strictures.
Methods: Two patients with ureteral stenoses underwent ureteral reconstruction with SIS matrix at the Zhejiang Provincial Corps Hospital of Chinese People’s Armed Forces between June 2014 and June 2016. The ureteral stenoses were repaired with a semi-tubular SIS matrix and the postoperative recoveries were observed.
Results: Both operations were successfully completed. The average operative time was 90 min and the average length of hospital stay was 15 days. No fevers, incision infections, intestinal obstruction, graft rejection, or other serious complications were noted. After 2 months, ureteroscopic examinations showed that the surfaces of the original patches were covered by mucosa and there were no apparent stenoses in the lumens. The ureteral stents were replaced every 2 months postoperatively and removed 12 months postoperatively. No infections or urinary leakage occurred after removal of the stents. Intravenous urography was performed 6 and 12 months postoperatively. The results showed that the ureters were not obstructed and there was no apparent stenosis at the anastomosis sites. The average follow-up time was >12 months. Long-term follow-up is still ongoing, and computed tomography examinations of the urinary tract have been conducted in the outpatient department of our hospital 1, 3,

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and 6 months after removal of the double-J stents, suggesting the absence of hydronephrosis. The serum creatinine levels remained stable during the follow-up.

**Conclusion:** SIS matrix reconstruction is a feasible method to repair ureters stenosis.

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1. Introduction

There are many causes of ureteral strictures, including congenital factors, abdominal and pelvic surgery, urinary calculi, retroperitoneal fibrosis, iatrogenic ureteral injuries, and idiopathic stenosis [1]. Current treatments for ureteral stenosis include intestinal ureters, autogenous kidney transplantation, endoscopic surgery, laparoscopic surgery, and biomaterial replacement of ureters. With the continuous development of tissue engineering, decellularized matrix as a scaffold for cell regeneration has gradually been adopted and has achieved a good clinical effect in the repair of long segmental urethral strictures [2]. Between June 2014 and June 2016, we applied a 4-layer overlapping decellularized small intestinal submucosa (SIS) matrix (Cook Co., Ltd. USA) to treat two patients with ureteral strictures, and good results were achieved.

2. Patients and methods

2.1. General information

Both patients were males. One patient was 62 years old and had idiopathic lower ureteral stenosis on the right side (3 cm in length). After 8 months of balloon dilatation, ureteral dilatation and hydronephrosis did not get better. The other patient was 51 years old. He underwent ureteroscopic lithotripsy for a right ureteral stone 2 years ago. Stenosis developed in the right middle ureter (2 cm in length) and right hydronephrosis occurred. A nephrostomy was performed after two unsuccessful endoscopic dilatations of the ureter. Both patients developed irritation and discomfort in the lumbar region of the affected side with mild renal function impairment. Systemic assessments were performed and no surgical contraindications were identified. The serum creatinine levels, glomerular filtration rates, intravenous urography findings, and ureteroscopic images were documented preoperatively. All procedures involving human participants were in accordance with the ethical standards of the Ethics Committee of Zhejiang Provincial Corps Hospital of Chinese People’s Armed Forces with the 1964 Helsinki Declaration and subsequent amendments or comparable ethical standards. Informed consent was obtained from both patients.

2.2. Surgical procedure

After general anesthesia was established, the patients were placed in the supine position with a slight lift of the hip. An oblique incision was made in the right lower abdomen and deepened layer-by-layer. The peritoneum was pushed internally and the ureteral tissue was carefully separated until the ureteral stenosis was exposed. The narrowed segment of the ureter was opened longitudinally and the length of the stenosis was measured. A double-J stent was implanted into the ureter along the guidewire, with one end in the renal pelvis and the other end in the bladder. A strip-shaped decellularized matrix matrigel (approximately 4.0 cm in length and 2.0 cm in width) was cut and the matrix was completely anastomosed to the opened ureter with 5-0 absorbable suture. The ureter was repaired with a semi-tubular shaped SIS matrix (Fig. 1). Two drainage tubes were placed adjacent to the anastomosis site. An indwelling bladder catheter was placed after the procedure.

2.3. Postoperative management and follow-up

The patients received broad-spectrum intravenous antibiotics for 7 days, followed by oral antibiotics thereafter until the drainage tubes were removed. The patients were evaluated every 2 months postoperatively. The double-J stents were replaced at the same interval until 12 months postoperatively. Flexible cystoscopy was carried out routinely 2, 4, 6, and 12 months after surgery. Intravenous urography was performed 2, 6, and 12 months after surgery. Computed tomography (CT) or B-ultrasound of the urinary system was performed in the outpatient department of our hospital 1, 3, and 6 months after removing the double-J tube.

Figure 1 Approximate procedure of operation. (A) Decellularized small intestinal submucosa (SIS) matrix; (B) Ureteral reconstruction in a semi-tubular style; (C) The SIS matrix was anastomosed to the opened ureteral wall. The white arrow is pointing at the SIS matrix; (D) The opened ureter was closed by SIS matrix.
3. Results

The operations were successfully performed in both patients. The formed matrix had a length of approximately 4.0 cm, with a width of approximately 2.0 cm. The average operative time was 90 min and the average hospital stay was 15 days. No fevers, incision infections, intestinal obstruction, graft rejection, or other serious complications occurred.

The presence of the implanted decellularized matrix was inspected under ureteroscopy 2 months postoperatively. The inner surfaces were covered with mucosa and the lumens at the anastomosis sites were slightly narrowed. The implanted decellularized matrices were partially degraded 4 months postoperatively and the ureteral stenoses were covered by mucosa. The lumens at the anastomosis sites were still slightly stenotic and the surfaces of the mucosa were rough. The acellular matrix patches were completely degraded 6 months postoperatively. The ureteral strictures were covered with mucosa, the lumens in the anastomoses were slightly narrow, and the surface mucous membranes were rough. Twelve months postoperatively, the matrices were completely degraded. There were no stenoses at the anastomosis sites and the mucosal surfaces were smooth and clean (Fig. 2).

The double-J stents were removed 12 months postoperatively and no infections or urinary leakage occurred thereafter. Urinary reassessment by intravenous urography showed no anastomotic stenoses along the ureters (Fig. 3). The patients have been followed up for >12 months. The serum creatinine levels postoperatively were similar to the levels preoperatively, and slightly above the normal range (Fig. 4). Long-term follow-up is still ongoing, and CT examinations of the urinary tract were conducted in the outpatient department of our hospital 1, 3, and 6 months after removal of the double-J stents with no signs of hydronephrosis.

4. Discussion

Ureteral stenosis refers to a variety of conditions (congenital malformations, injuries, inflammation, tumors, and retroperitoneal fibrosis). The ureteral lumen is narrowed in patients with ureteral stenosis, resulting in ipsilateral ureteral dilatation and hydronephrosis. In severe cases, irreversible renal function impairments, such as decreased renal filtration rate and renal atrophy occur [3]. Currently, endoscopic surgical treatment for ureteral...
stenosis is mainly performed in patients with stenosis <2 cm in length [4]. Such surgical procedures include balloon dilatation, rigid ureteral dilatation, ureteral stenting, and other surgical methods. For middle and long segment ureter strictures and defects, ureteral replacement surgery is needed to restore the integrity of structure and function. Therefore, the ideal alternative materials and the optimal surgical procedure still need to be determined by surgeons.

Alternative materials for the treatment of long-segment ureter strictures include the ileum, appendix, vesical-renal flap, lingual mucosa, oral and buccal mucosa, and tissue engineering materials; ileo-ureteral substitution is suitable for a wide range of ureteral lesions when there is no alternative [5]. Hyperchaotic acidosis, infections, secondary intestinal adhesions, and anastomotic stenosis are common. According to Obiaidah et al. [6], the small intestine or appendix as a Montix tube in children undergoing ureteral replacement therapy should be considered to replace the ureteral segmental defect; the outcomes are good, but there are few reports on the operation in adults. Due to the anatomic position, the appendix is often used to replace the right ureter, but there are limitations, such as secretion of mucus in the appendix, which can easily lead to infection. The location of the appendix, the length of the mesentery, the transfer of the appendix to the retroperitoneum, and the tension-free appendix cannot be determined preoperatively, and the length of the ureteral defect should be less than the length of the appendix. Substitution of the ureter with a bladder flap has achieved good clinical results; however, substitution of the ureter with a bladder flap is characterized by relatively large trauma, long operative time, and slow postoperative recovery, and good recovery of the postoperative bladder volume and urine reflux should be considered. Currently, substitution of the ureter with bladder flap is more common than replacement of urethal stricture or hypospadias with buccal mucosa, but substitution of the ureter with a bladder flap has rarely been reported in the treatment of ureteral strictures and the material source is limited. Repeated procedures can cause numbness in the mouth, difficulty opening the mouth, deflection of the lips, and secondary damage, and it is easy to damage the parotid duct opening, thus leading to impaired function of the salivary and parotid glands when taking materials. The acellular matrix patch (SIS) used herein was produced by Cook Co., Ltd., and is a commercial product approved by the US Food and Drug Administration. SIS is widely used in other tissues, including long urethral stricture repair, all of which have achieved good results [2]. SIS is a safe and practical bioengineering material, the safety of which is trustworthy.

SIS is a heterogeneous tissue derived from the small intestines of pig. SIS has the advantages of good cellular compatibility, biodegradability, and low immunogenicity. It has been shown that SIS consists of a variety of growth factors that can induce tissue repair, including fibroblast growth factor-2 and vascular endothelial growth factor [7]. SIS is biologically safe and functional, and has achieved good clinical outcomes in long segmental urethra reconstruction. It has been reported that in patients undergoing long segmental urethra reconstruction, the SIS matrix can be completely degraded 16 weeks postoperatively, and the anastomotic mucosa is intact and smooth [8]; however, there is limited experience involving the application of SIS in the reconstruction for middle and long ureteral stenosis and defects. In 2001, Liatsikos et al. [9] used a SIS matrix for repair of upper ureteral stenosis in female pigs. All animals survived for 7 weeks after surgery. Histological evaluation showed that ureteric epithelium regenerated on SIS and there was good neovascularization. There has been no evidence of SIS graft rejection to date. In a case report, O’Connor et al. [10] performed a tubular bridging anastomosis between the ureter and neo-bladder using a segment of swine small intestine submucosal tissue in a patient who failed multiple operative repairs for right ureteropelvic stenosis. Observations confirmed that the surrogate functioned well, and there was no leakage of urine at the anastomosis site and no stenosis recurred during the follow-up. Therefore, compared with autologous materials, such as tongue, cheek, and small intestinal mucosa, SIS patches have the advantages of convenient sampling, reduction of the supply area and postoperative complications, difficulty in rejection after transplantation, and facilitating cell growth by various growth factors and biodegradation.

The purpose of this study was to investigate the feasibility of repairing ureteral strictures with decellularized SIS matrix. As normal ureteral mucosa should be conserved as much as possible [11] to facilitate physiologic regeneration, the ureteral stenosis segment was only opened longitudinally without removal. The ureteral blood supply was also carefully protected. Combined with previous clinical studies on the repair of long-segment urethral defects, the lack of cells, tubular acellular tissue matrix, and various causes of cavernous fibrosis in urethral reconstruction could easily lead to postoperative urethral stricture recurrence or occlusion due to insufficient blood supply to support epithelial cell regeneration [12,13]. One of our patients with ureteral stenoses had a history of recurrent right and middle ureteral calculi 2 years prior. During surgery there were strictures in the upper and middle ureteral calculi. Multiple holmium laser lithotripsy and dilation were performed. The right hydronephrosis and ureteral stricture recurred postoperatively (approximately 2 cm in the stenosis). The other patient had a congenital ureteral stricture (approximately 3 cm in the stenosis). There was no significant improvement after performing multiple balloon dilations. Unlike traditional ureteral stricture resection and anastomosis, our team cut the ureter in the longitudinal section of the ureteral wall longitudinally instead of completely disconnecting the ureter, and then the long strip-shaped acellular matrix patch was completely anastomosed with the incision wall to make the patch a component of the ureteral wall and to enlarge the lumen diameter of the stenotic segment. Such a partial incision can conserve the normal ureteral mucosa, which can provide better blood supply, but not destroy the ureteral peristaltic wave conduction and maintain the integrity of the ureter. It is convenient for the tissue epithelial cells of
the peripheral ureter to migrate into and cover the replacement segment, laying a foundation for establishing a new blood circulation and promoting ureteral repair and reconstruction as soon as possible. Postoperative recovery was good and there were no severe complications. Postoperative follow-up showed no significant obstruction at the anastomosis site. Long-term follow-up is still ongoing, and CT examinations of the urinary tract were performed in the outpatient department of our hospital 1, 3, and 6 months after removal of the double-J stents, suggesting no obvious hydronephrosis. We conclude that SIS is a commercial product approved by the FDA, the application of which greatly reduces trauma and complications. SIS is indicated for patients with middle and long-segment ureter strictures who decline secondary procedures, and who relapse after repeated dilatation of the urethral stricture, but SIS should be carefully considered when being used for patients who have severe infections, complete ureteral occlusion, and who fail to provide postoperative blood supply for ureteral stenosis because of retroperitoneal fibrosis.

Due to the limited number of patients in this study, the risk of peri-operative complications, postoperative long-term efficacy, and the indications of this procedure warrant further study.

5. Conclusion

A SIS matrix can be used as an alternative material in reconstructive operations involving ureters. SIS matrix replacement is a feasible method to repair ureteral stenosis and the overall safety and long-term efficacy deserve further investigation.

Author contributions

Study concept and design: Qingkang Xu.
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Conflicts of interest

The authors declare no conflict of interest.

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References

[1] Ganzer R, Franz T, Rai BP, Siemer S, Stolzenburg JU. Management of ureteral strictures and hydronephrosis. Urologe 2015;54:1147–56.
[2] Xu YM, Fu Q, Sa YL. Outcome of small intestinal submucosa matrix for repair of anterior urethral strictures. Int J Urol 2013;20:622–9.
[3] Wein AJ, Campbell MF, Kavoussi LR. In: Campbe U-walsh urology. 9th ed. Philadelphia Saundem Elsevier; 2007. p. 1255–9.
[4] Streep NM, Nakada SY. Difficult case: ureteral stricture distal to a stone. In: Streep NM, Nakada SY, editors. Ureteral stone management. Switzerland: Springer International Publishing; 2015. p. 195–202.
[5] Owusu-Ofori K, Wilkinson E, Mellon WS, Nakada SY. A unilateral ureteral obstruction mouse model is applied to investigate the pathophysiology of obstructed ureters. J Urol 2009; 181:721.
[6] Obaidah A, Mane SB, Dhende NP, Acharya H, Goel N, Thakur AA, et al. Our experience of ureteral substitution in pediatric age group. Urology 2010;75:1476–80.
[7] McDevitt CA, Wildey GM, Catrone RM. Transforming growth factor-betal in a sterilized tissue derived from the pig small intestine submucosa. J Blimed Mater Res A 2003;67:637–40.
[8] Xu YM, Zhang J, Fu Q, Sa YL, Song LJ, Chao F. [Analysis of the efficacy of the small intestinal submucosal decellular matrix for the repair of anterior urethral stricture]. Chin J Urol 2011; 32:419–22. [Article in Chinese].
[9] Liatsikos EN, Dinlenc CZ, Kapoor R, Bernardo NO, Pikhasov D, Anderson AE, et al. Ureteral reconstruction: small intestine submucosa for the management of strictures and defects of the upper third of the ureter. J Urol 2001;165:1719–23.
[10] O’Connor RC, Patel RV, Steinberg GD. Successful repair of a uretero-neobladder stricture using porcine small intestine submucosa. J Urol 2001;165:1995–7.
[11] Li WH, Liu NB, Fang ZL, Zang MF. [Clinical application of allogeneic acellular dermal matrix for ureteral stricture]. J Clin Urol 2008;23:516–7. [Article in Chinese].
[12] Palminteri E, Berdondini E, Colombo F, Aousti E. Small intestinal submucosa (SIS) graft urethroplasty: short-term results. Eur Urol 2007;51:1695–701.
[13] El-Assmy A, El-Hamid MA, Hafez AT. Urethral replacement: a comparison between small intestinal submucosa grafts and spontaneous regeneration. BJU Int 2004;94:1132–5.