Penis Transplantation

First US Experience

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Objective: We describe the first successful penis transplant in the United States in a patient with a history of subtotal penectomy for penile cancer.

Background: Penis transplantation represents a new paradigm in restoring anatomic appearance, urine conduit, and sexual function after genitourinary tissue loss. To date, only 2 penis transplants have been performed worldwide.

Methods: After institutional review board approval, extensive medical, surgical, and radiological evaluations of the patient were performed. His candidacy was reviewed by a multidisciplinary team of surgeons, physicians, psychiatrists, social workers, and nurse coordinators. After appropriate donor identification and recipient induction with antithymocyte globulin, allograft procurement and recipient preparation took place concurrently. Anastomoses of the urethra, corpora, cavernosal and dorsal arteries, dorsal vein, and dorsal nerves were performed, and also inclusion of a donor skin pedicle as the composite allograft. Maintenance immunosuppression consisted of mycophenolate mofetil, tacrolimus, and methylprednisolone.

Results: Intraoperative, the allograft had excellent capillary refill and strong Doppler signals after revascularization. Operative reinterventions on postoperative days (PODs) 2 and 13 were required for hematoma evacuation and skin eschar debridement. At 3 weeks, no anastomotic leaks were detected on urethrogram, and the catheter was removed. Steroid resistant-rejection developed on POD 28 (Banff I), progressed by POD 32 (Banff III), and required a repeat course of methylprednisolone and antithymocyte globulin. At 7 months, the patient has recovered partial sensation of the penile shaft and has spontaneous penile tumescence. Our patient reports increased overall health satisfaction, dramatic improvement of self-image, and optimism for the future.

Conclusions: We have shown that it is feasible to perform penile transplantation with excellent results. Furthermore, this experience demonstrates that penile transplantation can be successfully performed with conventional immunosuppression. We propose that our successful penile transplantation pilot experience represents a proof of concept for an evolution in reconstructive transplantation.

Keywords: genitourinary vascularized composite allotransplantation, penis transplantation, reconstructive transplantation

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Vascularized composite allotransplantation (VCA) has become an established means of restoring complex soft tissue defects of the hand, face, and abdominal wall after extensive injury,[1–4] offering patients more optimal functional and physical restoration than conventional reconstructive options. Although initially met with ethical consternation, VCA has become widely accepted, and has resulted in excellent aesthetic and functional outcomes. Morbidity and mortality from these procedures is infrequent and has been almost uniformly due to sequelae or complications from the immunosuppressive medications required to prevent allograft rejection. Abrogation of the need for these drugs through induction of immunologic tolerance remains a critical focus of current research in this field.

Considering promising functional and psychosocial outcomes with other types of VCAs,[2] penis transplantation represents the next step in VCA evolution. Genitourinary injuries and diseases that result in partial or complete penile loss have devastating functional and emotional consequences for patients, leading to significant mental health sequelae, including depression and suicide.[5–7] Current reconstructive options for men with devastating genitourinary tissue loss are suboptimal in their ability to create a natural-appearing sensate phallus with sufficient voiding and erectile function.[8–11]

In 2006, the first penis transplantation was performed in China; however, the allograft was explanted 14 days postoperatively, reportedly due to psychological distress in the recipient.[12,13] The second was completed in December 2014 in South Africa with return of urinary and sexual function.[14]

We describe the first case of penis transplantation in the United States in a patient with a history of subtotal penectomy for penile cancer (Supplementary Table 1, http://links.lww.com/SLA/B229).

METHODS

The Genitourinary (GU)VCA pilot program at Massachusetts General Hospital (MGH) was initiated after institutional review board approval. The multidisciplinary team includes plastic surgeons, urologists, radiologists, pathologists, psychiatrists, transplant coordinators, nurses, social workers, dieticians, and financial coordinators. Evaluation of the patient began with extensive education and informed consent. Preoperative assessment included routine blood work, infectious disease screening, cardiovascular evaluation,

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pretransplant human leukocyte antigen (HLA) panel reactive antibodies, and detailed imaging (see below). Based on negative T-cell and B-cell cross-matches, skin color, and other characteristics, a brain-dead donor was identified by the New England Organ Bank (Supplementary Table 1, http://links.lww.com/SLA/B229).

Preoperative Imaging Protocol

High-resolution computed tomography angiogram (CTA), diagnostic angiography, and magnetic resonance imaging (MRI) of the pelvis and penis were performed. CTA allows for volumetric and multiplanar analysis of the arterial vasculature that is critical for preoperative planning (Fig. 1). In some cases, CTA may replace invasive diagnostic angiogram for aorta, iliac branches, internal pudendal artery branches, and other small arterial branches. However, depending on the patient's anatomy and underlying history, CTA may have limited resolution for smaller vessels such as the dorsal penile, bulbar, and cavernosal arteries. Diagnostic angiography has an advantage in these situations where smaller vessels are not well-characterized on CTA (Fig. 2). MRI of the pelvis and penis allows for the characterization of the soft tissue including the corporal bodies, and also the pudendal nerves and their branches. The spatial resolution of MRI is limited, but tissue contrast is superior to CT in this application; however, with isometric high-resolution sequences, there is the opportunity to characterize and confirm the presence of neurovascular bundles (Fig. 3). The combination of these 3 complementary imaging modalities allows for both evaluation of transplantation candidacy and surgical planning.

Transplantation Procedure

One surgical team procured the donor allograft, whereas the other prepared the recipient. The allograft was harvested with bilateral fasciocutaneous flaps to preserve the external pudendal vessels to the femoral vessels. Amputation at the pubic bone preserved maximal corporal and urethral length. The dorsal penile arteries and nerves, cavernosal arteries, and deep dorsal vein were preserved (Fig. 4). Concurrently, the right groin and penile stump of the recipient were dissected to expose the critical nerves and vessels paralleling the allograft (Fig. 5).

Reconstructive transplantation began with a spatulated urethral anastomosis followed by approximation of the corporal bodies which prepared the scaffolding for the delicate neurovascular anastomoses (Fig. 6). The cavernosal arteries and deep dorsal vein were anastomosed primarily with standard microsurgical technique (Fig. 7 and Supplementary Fig. 8, http://links.lww.com/SLA/B229). Due to sclerotic recipient dorsal arteries, a vein graft was harvested from the distal leg and anastomosed end-to-side to the right femoral artery and end-to-end to the right dorsal penile artery (Supplementary Fig. 9, http://links.lww.com/SLA/B229). Cadaveric acellular nerve allograft was used to bridge a 2-cm gap between the dorsal penile nerves of the recipient and allograft with standard epineural neurorrhaphies. As the penile allograft was clinically well-perfused with the dorsal and cavernosal arterial anastomoses, we elected to forgo anastomosis of the external pudendal artery and resected excess proximal pubic skin from the allograft. A Foley catheter was used to protect the urethral reconstruction and bulb suction drainage was placed to the right groin vascularized composite tissues (Supplementary Fig. 10, http://links.lww.com/SLA/B229 demonstrates pretransplantation and posttransplantation photographs; full details of transplantation procedure can be found in the Supplemental Appendix, http://links.lww.com/SLA/B229).

Immunologic Management

The patient underwent induction with rabbit antithymocyte globulin (ATG), mycophenolate mofetil (MMF), and methylprednisolone before allograft perfusion. Maintenance immunosuppression consisted of MMF, tacrolimus, and prednisone taper. Punch biopsy samples were obtained during suspected rejection episodes and graded according to the 2007 Banff scale.[15] Immunosuppression was adjusted based on clinical assessment, skin biopsy results, and tacrolimus trough levels (Supplementary Figs. 11 and 12, http://links.lww.com/SLA/B229). Trimethoprim-sulfamethoxazole and valganciclovir were initiated as prophylaxis against *Pneumocystis* sp. and cytomegalovirus.

RESULTS

Postoperatively, the allograft had excellent capillary refill and strong Doppler signals. Intravenous (IV) vancomycin, piperacillin/tazobactam, fluconazole, oral vancomycin, and IV heparin were administered in the postoperative period. The patient returned to the operating room on postoperative day (POD) 2 for hematoma evacuation and was given 2 units of packed erythrocytes. Tadalafil 2.5 mg daily was initiated on POD 8 to therapy for erectile conditioning. On POD 13, a small eschar on the superior aspect of the skin flap required operative debridement. The patient's catheter was

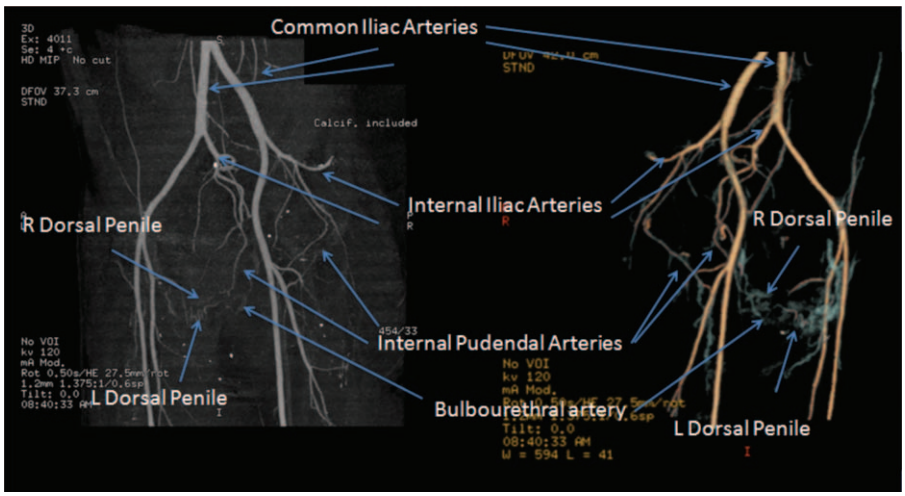

FIGURE 1. High-resolution CT angiography with 3D reconstruction.

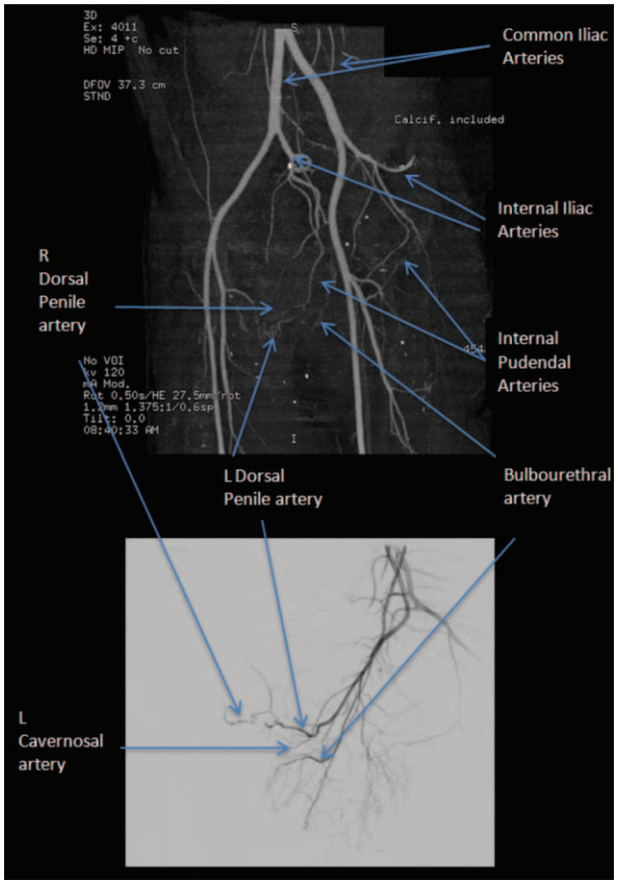

FIGURE 2. CT angiography and conventional angiography.

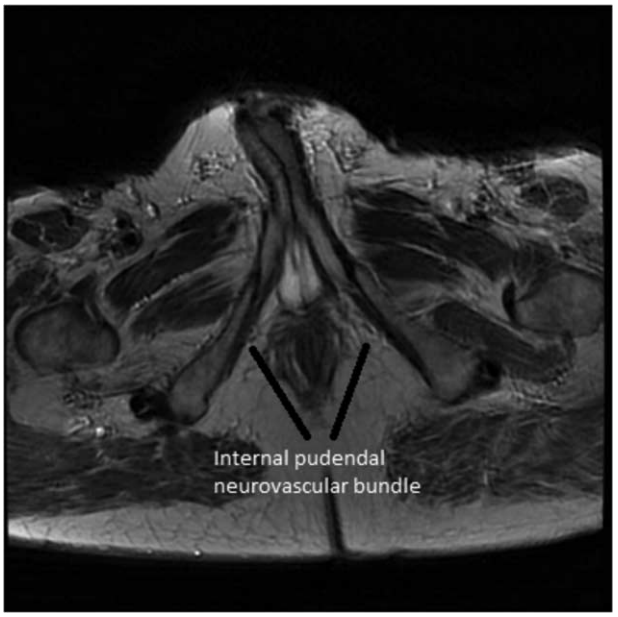

FIGURE 3. Pelvic MRI.

removed 3 weeks postoperatively after a retrograde urethrogram demonstrated a normally healed urethra without anastomotic leakage. He was able to void immediately with excellent urinary stream and was subsequently discharged on POD 25.

On POD 28, erythema of the allograft was clinically diagnosed as acute rejection. The allograft skin was biopsied and rejection was confirmed on histopathology. The allograft punch biopsy sample showed focal perivascular inflammation in the deep dermis with minimal superficial dermal inflammation. An arteriole showed transmural mononuclear inflammation with focal karyorrhexis. A peri-eccrine lymphocytic infiltrate and focal panniculitis were also present. The epidermis did not show lymphocytic infiltrate or keratinocyte apoptosis. The immunohistochemical stain for C4d was negative. This is grade I rejection in the 2007 Banff classification, which does not include vascular inflammation.[16] The rejection episode was treated with 2 pulse doses of methylprednisolone. After initial clinical improvement, recalcitrant erythema was observed on POD 32. A second biopsy showed mild perivascular mononuclear inflammation of the superficial and deep dermal vessels. Focal endothelialitis was present in 1 artery. Veins and venules also showed focal inflammation within and along the wall. The epidermis showed a few foci of keratinocyte apoptosis and lymphocytic infiltration. A peri-eccrine lymphocytic infiltrate and panniculitis with fat necrosis were also

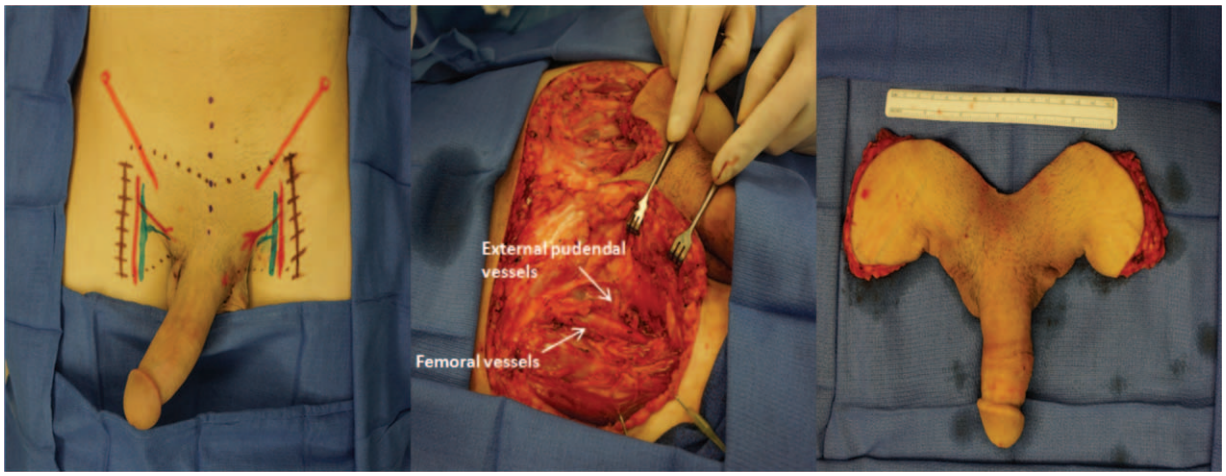

FIGURE 4. Allograft procurement.

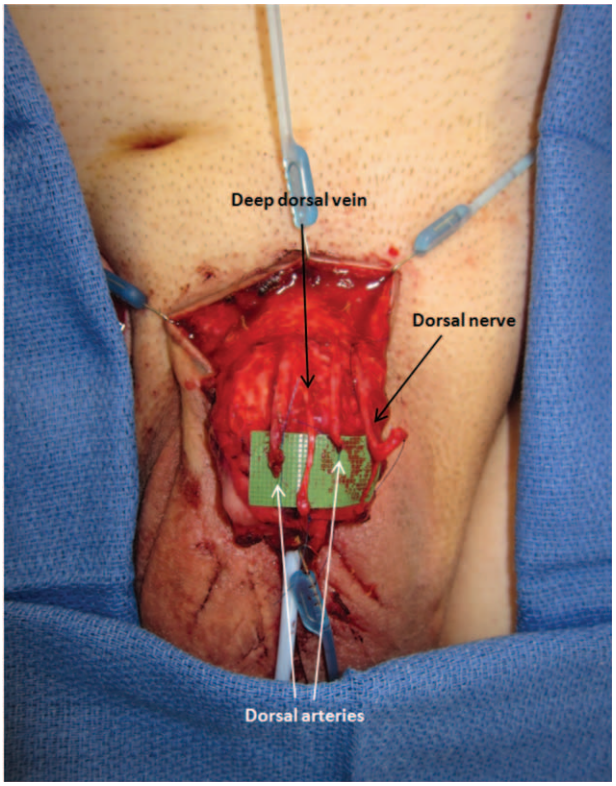

FIGURE 5. Recipient anatomy.

present. The C4d stain was again negative; however, CD3+ T cells were detected in the epidermis and perivascular spaces, and were prominent in the area with panniculitis. The presence of epidermal involvement raised the Banff grade to III (Supplemental Appendix, http://links.lww.com/SLA/B229). He was then treated with a repeat course of ATG for 4 days and 2 pulse doses of methylprednisolone on consecutive days. This was followed by an oral prednisone taper to a baseline dosage. This regimen resulted in complete resolution of rejection. A detailed event timeline is provided in the Supplemental Appendix (http://links.lww.com/SLA/B229).

At 6 months postoperatively, the patient describes recovered sensation in the proximal penile shaft. He voids with excellent stream and low postvoid residual volumes. In addition, he has reported spontaneous partial erectile function with increasing quality and frequency.

DISCUSSION

The need for better reconstructive options after genitourinary tissue loss due to cancer or trauma is clear. The success of other VCAs (eg, hand and face transplants) performed has raised the possibility of introducing other complex soft tissue transplants, such as GUVCA, to the reconstructive armamentarium. The ethics of performing nonlife-saving VCA has been a challenging intellectual and thoughtful ethical debate over the years. The field of transplantation has accumulated over 60 years of experience with the use of immunosuppressive agents and continued to foster the proper utilization of newer and more potent pharmacologic agents to achieve better and safer patient outcomes for the future. At the same time, it is abundantly clear that the side-effect profiles of these lifelong medications can be problematic and have adverse clinical outcome

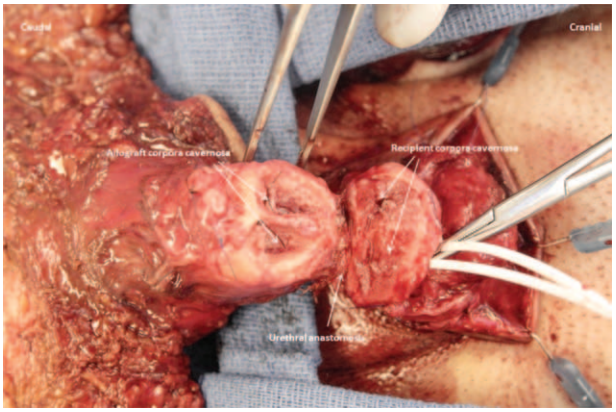

FIGURE 6. Corporal anastomosis.

implications.[17] However, the risk and benefit ratios accepted by the medical community and the patients are based on a principle that nonintervention or nontreatment can be far worse than that of the drugs themselves.[18]

At the beginning of the new paradigm in reconstructive transplantation, ethicists have rightly challenged the audacity of performing nonlife-saving transplantations with a goal for vanity and appearance rather than preservation of life itself. These procedures are directly against the principal precepts of the Hippocratic Oath in "primum non nocere." Nevertheless, the argument for reconstructive transplantation is that the sanctity of life, and thus living, is more far-reaching than what organs such as kidney, liver, or heart can provide. That is, the face, the hand, the genitals are all functional pieces that allow us to live in the most productive way that we can, harnessing from science and the dictum of reconstructive plastic surgery that the best way to repair what's missing is to replace "like with like." Reconstructive transplantation is a holistic approach to allow individuals to retain a normalcy of human existence that is not otherwise achievable without it. The ethical debate, in a very short time, has evolved dramatically from outright objectionable to feasible for the most gruesomely disfigured.[19] It is logical, with assurances to the scientific community, that consensus guidelines can be established to foster the approaches of the innovators to ensure that the clinical applicability of such novel work can be ethically applied.[20] With the recent regulatory categorization of VCAs as organs by the Organ Procurement and Transplantation Network,

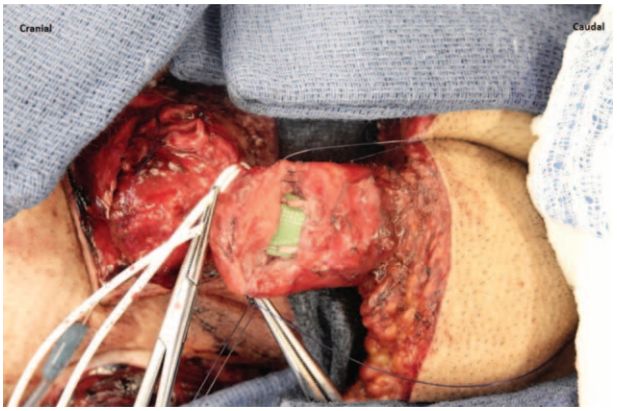

FIGURE 7. Cavernosal artery anastomoses.

VCA programs now have a context and regulatory framework to guide such transplants.

Morgenstern discussed innovative surgery's dilemma in which there must be transparency in laboratory background, field strength, and institutional stability to justify ethical approaches to changes in paradigm.[21] Institutional Review Board (IRB) directed research, such as the penile VCA protocol, highlights the critical level of thought and accountability that goes into the informed consent process at an individual institutional level.[22] We have gained much knowledge from our colleagues who have pursued VCA in the upper extremity, face, and now penile transplantation that can add insight into the question of the long-term effects of immunosuppression in the setting of reconstructive transplantation. Indeed, the penile VCA literature has only 3 such cases performed in the world; yet this work has already provided us with information to address the concerns of long-term immunosuppression in the setting of penile transplantation, thus allowing us to convey this information to potential penile VCA candidates. It is necessary to continue to perform these operations under IRB protocols such that valid data will be collected and shared with the scientific community. In doing so, the field of transplantation for genitourinary reconstruction can follow the preliminary recommendations in the ethics of penile transplantation.[23]

Each GUVCA recipient must be evaluated on an individual basis, given the potential for tremendous variation with respect to the degree of tissue loss. Appropriate preoperative evaluation and counseling by a multidisciplinary transplant team is paramount. In addition to our stringent selection criteria developed for penile transplant candidacy, justifications to our IRB were made for our recipient who is a penile cancer survivor. In a large series of 700 patients with penile cancer, 98.5% of all regional lymph node recurrences and 100% of all distant recurrences occurred within 4 years. In this reported series, 84.6% of all local recurrences occurred within 4 years, but the vast majority of local recurrences in this series occurred in men who underwent penile-preserving treatment. The overall local recurrence rate after nonpenile-preserving surgery, including both partial or total penectomy, was only 5.3%, with the majority of those occurring within 4 years.[24] Therefore, in our patient who underwent a partial penectomy and had remained disease-free for 4 years, the risk of regional or distant recurrence is 1.5% or less. His risk of local recurrence is negligible, given that his remaining native penile skin was resected at the time of transplant.

Despite meticulous preoperative planning, there were unexpected intraoperative findings. Studies have reported that penile transplantation would require multiple arterial anastomoses.[25] However, we were able to establish excellent flow to both the penis and skin flap via the cavernosal arteries and a single dorsal artery using a vein graft, which suggests that the robust collateral circulation of the penis may have been previously underestimated. We were able to determine allograft perfusion intraoperatively by color, venous backflow, capillary refill, and Doppler signals. The presence of a nerve gap presented an additional challenge in the context of VCA that was addressed using a commercially available acellular nerve allograft.

Our patient's postoperative course was complicated by unplanned but anticipated operative procedures for hematoma evacuation and small wound debridements, and also an episode of steroid-resistant acute rejection which necessitated additional T-cell depletion therapy.[26] Although there remains no consensus on the optimal treatment regimen for acute rejection episodes in VCA,[27] we have demonstrated success using standard VCA immunosuppression.[28] Although our patient will require lifelong immunosuppression subjecting him to the potential systemic complications,[2] we are actively developing novel protocols to induce immune tolerance of VCAs.[29] Successful clinical translation will enable complete immunosuppression withdrawal while avoiding the specter both acute and chronic rejection of VCAs.

Our case of penis transplantation demonstrates that GUVCA represents a viable option for restoration of normal external genital appearance, urinary, and potentially sexual function after genitourinary tissue loss. At 6 months postoperatively, our patient has recovered normal appearance of the penis, full urinary function, and partial sensory and erectile function. Perhaps, more importantly, our patient reports increased overall health satisfaction, dramatic improvement of self-image, and significant optimism for the future.

In conclusion, on the basis of our initial experience, we have shown that it is feasible to perform penile allotransplantation with excellent initial results. Despite early surgical and immunological events and a relatively short follow-up, this study provides proof of concept that GUVCA can restore functional defects and improve one's self-image. Furthermore, this experience demonstrates that GUVCA can be performed using conventional immunosuppression and acute rejection episodes successfully managed. GUVCA represents a new paradigm in restoring anatomic appearance and genitourinary function after genitourinary tissue loss and constitutes an encouraging evolution in reconstructive transplantation.

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