Journal of the American Association for Laboratory Animal Science
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Vol 53, No 5
September 2014
Pages 523–527

Clinical Allograft of a Calcaneal Tendon in a Rhesus Macaque (*Macaca mulatta*)

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A 5.5-y-old male rhesus monkey (*Macaca mulatta*) housed in an outdoor field cage presented for severe trauma involving the left calcaneal tendon. Part of the management of this wound included an allograft of the calcaneal tendon from an animal that was euthanized for medical reasons. This case report describes the successful medical and surgical management of a macaque with a significant void of the calcaneal tendon. To our knowledge, this report is the first description of a successful tendon allograft in a rhesus macaque for clinical purposes.

Abbreviation: CNPRC, California National Primate Research Center.

To facilitate psychologic wellbeing, rhesus macaques in breeding colonies are commonly housed in large outdoor social groups. This housing strategy offers environmental enrichment by enabling animals to interact socially and have access to large enclosures with diverse substrates and best mimics the environment of free-living macaque species.[17] However, rhesus macaques are known as a "belligerent species,"[11] and conspecific trauma is common with this housing strategy.[4,21] Medical and surgical management of conspecific trauma from outdoor housing represents one of the several challenges facing veterinarians working with this species. Here we describe the repair of a calcaneal tendon in an adult rhesus macaque after traumatic destruction of the tendon due to wounding from conspecifics. Surgical management involved allografting a tendon from another animal of the same species.

Case Report

The subject of this case report is a male rhesus macaque (age, 5.5 y; weight, 11 kg). This animal was housed in an outdoor field cage at the California National Primate Research Center. Field cages at this facility are each half acre in size; demographics within the field cages are mixed ages and sexes, as is considered standard for outdoor breeding colonies of this species.[33] All animals at the center are housed in accordance with AAALAC and USDA standards.[1,2,17] The viral status of this macaque was considered to be 'conventional,' in that cohorts are periodically screened and have tested negative for SIV and simian retrovirus. Conventional animals are considered to be positive for macacacine herpesvirus B, and colony surveys indicate a low prevalence (approximately 5%) of simian T-cell lymphotrophic virus.

On 12 October 2012, this macaque presented to the facility hospital from one of the described outdoor enclosures for severe trauma to the soft tissues around the left tibiotarsal joint and caudal portion of the left gastrocnemius muscle. The original wound was suspected to have been caused by bite wounds from conspecifics, which punctured the soft tissues around the distal region of the left leg. The original wound was undetected earlier during daily health assessments likely due to its size and the fact that it was well covered by the animal's hair coat. We surmised that this untreated wound then abscessed and ruptured. Once the wound was observed, the animal was brought into the hospital for veterinary care.

A complete physical exam, wound assessment, and treatment were performed under sedation with ketamine (10 mg/kg IM; ketamine hydrochloride, Bioniche Pharma, Rosemont, IL). The wound, located just proximal to the left tibiotarsal joint, was approximately 8 × 10 cm in size and involved the calcaneal tendon. Skin edges, calcaneal tendon, and surrounding soft tissues of the wound were necrotic, and purulent discharge was present. During the time of the initial presentation, all nonviable tissue was surgically debrided from the wound. The proximal end of the calcaneal tendon was identified and labeled with nonabsorbable suture material to facilitate future identification of the tendon remnant. No initial wound culture was taken, and the animal was empirically treated with metronidazole (50 mg/kg SC daily; US Compounding Veterinary Pharmacy, Conway, AR) and cefazolin (25 mg/kg IM twice daily; Ancef, GlaxoSmithKline, Research Triangle Park, NC). Ketoprofen (2 mg/kg IM daily; Ketofen, Fort Dodge, Fort Dodge, IA) was given for analgesia and to reduce inflammation surrounding the wound. The macaque was hospitalized indoors in an individual squeeze-back cage for ongoing wound care. During this time, the macaque was assessed daily for awareness, activity, responsiveness, appetite, hydration, and stool quality. These parameters remained within normal limits for this animal for the duration of hospitalization.

The wound initially was managed by using wet-to-dry bandages, which were changed daily under ketamine sedation, for complete debridement of the wound. At the time of each bandage change, the wound was lavaged copiously with chlorhexidine solution diluted with 0.9% saline. Approximately 5 d later, debridement was complete. At this time, calcium alginate bandages (Curasorb, Kendall, Covidien, Mansfield, MA) were used and changed daily under ketamine sedation to enhance tissue granulation and to keep the wound free from contamination until the time of surgical repair. Seven days after initial presentation, sufficient healthy granulation tissue was present, and the wound no longer contained any necrotic tissue. By visual assessment, there was an approximately 30% (or 5 cm) deficit of the most distal portion of the calcaneal tendon.

Received: 23 Apr 2013. Revision requested: 10 May 2013. Accepted: 04 Feb 2014.
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Given the size of the tendon deficit, a tendon allograft was the treatment of choice for this case.[35] A suitable donor was identified among animals being culled from the colony for medical reasons, and the recipient animal was scheduled for tendon allograft surgery the following day.

The donor was an unrelated 6-y-old mature male rhesus macaque, also of conventional viral status, scheduled for medical cull due to chronic diarrhea. The donor was euthanized (100 mg/kg pentobarbital IV; Fatal-plus, Vortech Pharmaceuticals, Dearborn, MI), and the donor tendon was surgically harvested as outlined in the literature.[25] Immediately after euthanasia, the skin over the left calcaneal tendon was aseptically prepared,[28] and an approximately 7.0-cm longitudinal posterolateral incision of the skin was made over the harvest site. The calcaneal tendon was exposed by using blunt and sharp dissection (Figure 1). The proximal calcaneal tendon was severed about 1 to 2 cm distal to the gastrocnemius muscle. The tendon was freed from underlying tissue by using blunt and sharp dissection, up to the point of insertion into the posterior tuberosity of the calcaneus bone. Harvest of an approximately $1 \times 1 \times 1$ cm portion the posterior tuberosity of the calcaneus bone was facilitated by using a Luer bone rongeur. The resulting 5 cm length of harvested calcaneal tendon and calcaneus bone was removed en bloc and immersed in 0.9% sterile saline in a sterile surgical bowl (Figure 2). The donor tendon was stored, at room temperature, for approximately 1 h in the surgical suite while the recipient animal was prepared for engraftment.

The recipient macaque was sedated with ketamine and atropine (0.05 mg/kg IM, Baxter HealthCare, Deerfield, IL), intubated, and maintained at a surgical plane of anesthesia by using isoflurane (1.5% to 2%, Piramal Critical Care, Bethlehem, PA). The surgical site was prepared by using standard techniques.[28] The recipient was prepared for engraftment according to the following technique.[35] Under aseptic conditions and with the patient in prone position, approximately 2 to 3 cm of the proximal skin wound was sharply dissected and retracted to facilitate visualization of the distal gastrocnemious muscle and proximal portion of the calcaneal tendon. The identification suture previously placed in the proximal remnant of the calcaneal tendon was isolated and removed. The proximal remnant of the calcaneal tendon was released from adhesed adjacent tissue by using blunt and sharp dissection. The distal most edge of the tendon was partially frayed, and therefore stray fragments were sharply dissected and removed. The remaining proximal tendon then was lavaged with sterile saline and manually wiped with sterile gauze to assure removal of any remaining fibrin deposits. At the distal portion of the wound, the calcaneus bone was easily visualized without additional skin dissection. The posterior tuberosity of the calcaneus bone was surgically exposed by using blunt and sharp dissection to remove granulation tissue. The calcaneus bone was copiously lavaged with sterile saline and wiped clean with sterile gauze. The joint capsule around the tibiotarsal joint had been intact at the time of initial injury and was not disturbed at the time of surgery.

After complete surgical preparation of the recipient for engraftment, the deficit was thoroughly assessed again. The distal 30% (approximately 4 to 5 cm) of the calcaneal tendon was nonexistent, with complete avulsion away from the calcaneus bone. After the recipient was prepared for engraftment, the donor tissue (posterior tuberosity of the calcaneus bone and attached calcaneal tendon) was removed from the sterile saline. The tissue for engraftment was placed in the area of deficit of the recipient; the distal portion of the graft was the first area to be surgically secured. The harvested posterior tuberosity of the calcaneus bone was anchored to the posterior tuberosity of the calcaneus bone of the recipient with 2 Kirschner pins (size, 1/16 in.). The Kirschner pins were used to mechanically anchor the graft bone to the recipient bone and to partially stabilize the engrafted tendon. To provide further stabilization of the distal portion of the graft, the medial and lateral portions of the harvested calcaneal tendon were sutured to adjacent granulation tissue, presumably associated with underlying retrocalcaneal bursa, by using 3-0 polypropylene suture material in a simple interrupted pattern.

Figure 1. Surgical exposure of harvest tendon from allograft donor.

Figure 2. Harvested calcaneal tendon en bloc. Bar represents 1 cm. Figures 1 and 2 are representative of donor tissue and not photos taken of the actual donor listed in this article.

After the distal portion of the graft was secured, the next surgical step was to secure the proximal portion of the graft in the recipient as described previously.[35] Using 1-0 polypropylene suture material, Krackow sutures were placed in the distal portion of the proximal calcaneal tendon of the recipient and, by using the sutures ends as a grasping point, gentle manual traction was applied to the recipient tendon. Subsequently, 1-0 polypropylene suture material in a Krackow suture pattern was placed in the proximal portion of the donor tendon. The 2 ends of Krackow sutures were then tied together and secured under physiologic tension to facilitate anastomosis of the donor and recipient tendon. At this time, the engrafted tendon did not lie flat as expected anatomically; the tendon edges curled medially. For this reason, additional tendon stabilization was attempted. The medial and lateral portions of the engrafted tendon were tacked to granulation tissue covering the soleus muscle by using 3-0 polyglactin 910 suture material in a simple interrupted pattern. This addition to the published surgical technique provided enhanced placement to keep the engrafted tendon in the correct anatomic position. The subcutaneous tissue surrounding the surgical wound was apposed by using 3-0 polyglactin 910 in a simple interrupted pattern. The skin was partially apposed

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by using polyglactin 910 in a horizontal mattress pattern. Due to the lack of sufficient viable skin secondary to the wounding incident, a skin deficit (approximately 0.5 cm by 0.2 cm) was present postsurgically at the center of the surgical site. The surgeons elected to allow this portion of the skin to close by second-intention healing.

Immediately after surgery, the wound was covered with a nonadherent dressing (Telfa Plus Island Dressing, Covidien), and the leg was bandaged with a modified Robert–Jones bandage to immobilize the joint in a midflexion position. This position was chosen to prevent bandage removal and to keep mild tension on the engrafted tendon.[25]

Postoperatively, the macaque was housed in a standard primate cage (6 ft^2 × 32 in.) and treated with oxymorphone (0.15 mg/kg IM 3 times daily; Opana EndoPharmaceuticals, Huntsville, AL). Cefazolin and ketoprofen were restarted as previously described. The bandage was changed under ketamine sedation every 1 or 2 d, depending on its integrity. At the time of each bandage change, the wound was assessed for heat, swelling, erythema, or discharge. Ten days after surgery and after completion of antibiotic therapy, the skin incision partially dehisced, and moderate purulent discharge was noted. Cytology of the discharge demonstrated large numbers of neutrophils and a few gram-positive bacteria. These results were consistent with normal skin contaminants and did not indicate tissue rejection. The wound was cultured (aerobic and anaerobic), and empirical treatment was reinitiated with metronidazole and cefazolin as previously described. Culture results revealed 4+ coagulase positive *Staphylococcus* spp. and 4+ *Corynebacterium* spp. These results indicated that no change in antibiotic therapy was needed. Wound care continued as described, with the addition of lavage with chlorhexidine solution diluted with 0.9% sterile saline and wet-to-dry bandages to facilitate removal of purulent discharge of the site. Once debridement was complete, the site was covered with calcium algenate bandage to promote granulation for approximately 5 d, after which the site was covered with a nonadherent bandage to promote epithelization until the affected area was completely healed, at approximately 24 d after surgery. At 16 d postoperatively, a single Kirschner pin was visible at the wound edge. This Kirschner pin was removed under ketamine sedation at the time of wound care and bandage change. The second Kirschner pin was not removed and remains in the patient.

Approximately 1 mo after surgery, the dehisced surgical site was healing well by second intention, and the macaque began bearing weight on the limb. Leg use was encouraged by periodically (approximately 3 times each week) allowing the animal access to an outdoor exercise enclosure. By approximately 6 wk postoperatively, the macaque was walking, running, and climbing without any noticeable deficit of the left leg. There was no observable plantigrade stance or loss of function in the limb. The patient was assessed as having full function of the leg and was scheduled for return to outdoor housing.

Approximately 10 mo after the engraftment surgery, the macaque was brought into the hospital facility from outdoors for physical examination of the surgical site. The animal was sedated with ketamine (10 mg/kg), and a complete exam was performed. The macaque was in good flesh, and there was no appreciable muscle atrophy of the affected limb. The engrafted tendon was readily palpable and was thickened at the region of proximal anastomosis. The left tibiotarsal joint was easily flexed to 92° and extended to 155° with the left stifle joint in full extension. For comparison, measurements of the right leg were taken as well. The right tibiotarsal joint flexed to 82° and extended to 155° with the right stifle joint in full extension. The macaque was considered fully healed and was returned to its home cage.

Discussion

Social housing of rhesus macaques in breeding facilities such as this center is unique in that large groups of animals (60 to 120) are housed together in half-acre outdoor enclosures (field cages). This practice allows for development of the normal social hierarchy and interactions that this species may experience in the wild,[11] provides opportunities for engagement with animals of various ages, and encourages self-motivated exercise through freedom of movement within the enclosure. Housing in this manner is an effective and efficient method of animal production, allowing macaques to breed naturally and raise their own offspring. In addition, social housing is considered imperative to the psychologic wellbeing of nonhuman primates and is mandated by regulatory agencies such as USDA and AAALAC,[10,42] given that nonhuman primates are considered a social species by nature.[11,20,43] There are risks, however, associated with social housing that include matrilineal overthrows, intermale aggression, breeding traumas, and conspecific wounding.[33]

Conspecific trauma represents a serious threat to nonhuman primate health and longevity and involves a considerable investment in clinical resources for large-scale breeding facilities. Specifically, males are known to fight at increased rates during the breeding season[4,21] and, due to their large canine teeth, can inflict severe, life-threatening wounds in a single altercation. Extensive muscle and tendon injuries are common sequelae of these interactions and can result in significant morbidity, mortality, and loss of genetic diversity within the breeding colony.[33]

Severe injuries, such as tendon laceration and necrosis, present challenges in case management, surgical approach, and surgical expertise and may result in prolonged in-patient care. This level of skilled medical care often necessitates methods not often encountered in indoor-housed laboratory animals. Severe wounding may result in permanent relocation to indoor housing or, in some instances, euthanasia of the animal, with the subsequent loss of a potentially valuable research subject and its unique genetic contribution to the breeding colony. The development of techniques such as cadaver harvest and allografting serve to increase the potential treatment options for interventional care and provide a means for preserving animal resources.

In humans, the calcaneal tendon (also known as the Achilles tendon) is the strongest and thickest tendon in the body.[35] Loss of function of this tendon leads to significant decrease in plantar flexion strength, leading to an inability to run, stand in plantar flexion (on tiptoe), and play sports and cause difficulty in climbing stairs.[26] Tendon rupture occurs most commonly in adults 30 to 50 y of age.[32] Rupture during sporting events is common,[30,32] and men are more often affected than are women.[16,30] Because Achilles tendon rupture is a frequently experienced human medical problem, several methods of repair of the ruptured tendon have been described, including nonsurgical repair,[16] autologous tissue grafts,[29] allogenic tissue grafts,[32] and repair using synthetic materials.[15] Although there is controversy over the best treatment for calcaneal tendon rupture in humans,[16] recommendations for treatment are often based on the time from injury to initiation of treatment.[6] Acutely diagnosed and treated ruptures tend to heal well with conservative therapy, whereas surgical repair of a neglected ruptured calcaneal tendon is considered the treatment of choice.[6,16,25] Although surgical repair decreases the incidence of re-rupture and deep-vein thrombosis,[16] it is associated with a higher wound complication rate than are nonsurgical treatment options.[22]

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Successful repair of tendon injuries represents a unique challenge, in that this tissue has a limited blood supply, and adhesions are readily formed during the healing process. The calcaneal tendon does not have a true sheath but is surrounded by a paratenon that has an extrinsic blood supply. During healing, fibroblasts from the paratenon invade the damaged areas between tendon ends, where they synthesize collagen.[5] This process continues for several weeks, eventually leading to secondary remodeling and increased tensile strength at approximately 20 wk after injury. In addition, minimizing adhesions and scar formation is critical, because their presence may severely restrict the tendon's ability to glide, which allows for normal movement of the limb. Appropriate surgical approach and tissue handling are paramount in reducing the risk of adhesions during end-to-end tenorrhaphy. Postoperative requirements include immobilization for 2 to 3 wk, followed by restricted activity for 3 wk and then a gradual return to normal activity. However, if the ends cannot be well apposed or if the postoperative care is compromised, scar formation occurs, resulting in decreased tensile strength in the area and increasing the risk of reinjury.[5]

In situations where a deficit of the tendon creating a gap of greater than 5 cm is identified, an autograft or allograft is considered.[35] Although tendon rupture in humans is common, only a single case report of a human receiving treatment for complete tendon deficit is available.[32] This patient had tendon rupture, postoperative complications, and wound infection, which resulted in a tendon defect that was surgically repaired by using a biostatic tendon allograft.[32] The principal function of a biostatic tissue allograft in the recipient's body is as scaffolding for regenerating tissue, thus retaining space for the recipient's own new cells.[31,34] Biostatic grafts are acellular, a characteristic that makes them an ideal allograft, because they can be stored for a long period of time, sterilized, and used without risk of inducing an immune response.[34] After implantation, the allograft gradually degrades, releasing chemotactic factors. These chemotactic factors attract recipient cells which migrate onto the graft, grow, differentiate, and initiate synthesis of extracellular matrix. Eventually the biostatic allograft is decomposed and replaced by the recipient's own tissue.[34]

Another option for ligament and tendon repair is to use an allograft harvested from a cadaver. A risk factor associated with same-species allografts is host rejection due to the immunogenicity of the implanted tissue. Decellularization of the host cells present in the tissue, to reduce immunogenicity prior to implantation, is accomplished by several methods categorized as physical, chemical, or enzymatic.[13] However, such treatments can affect the composition and mechanical behavior of the biologic scaffolds and are not consistently 100% effective.[7,12,13,37,38,45]

An additional advantage of some physical methods of decellularization, such as freeze-drying or freezing, is that in situations where fresh donor tissue is not readily available, tissues from prospective donors can be harvested and then freeze-dried or deep-frozen for use at a later time.[18] However, such processes can affect the biomechanical and structural performance of the allograft,[27,36] because intracellular ice crystals form, causing cell lysis, that can affect the extracellular matrix[13].

In the case we present here, simple tenorrhaphy could not be performed, due to a deficiency of viable calcaneal tendon. Because hindlimb impairment and inability to bear weight would result in this animal's exclusion from our outdoor colony, other options for repair were considered. Synthetic replacements such as polypropylene mesh were not considered due to the risk of rejection, infection and self-mutilation given the the nonhuman primate's ability to access the surgical site. Biologic implants from other species, such as porcine small-intestinal submucosa, were not considered due to the inherent risks that xenografts pose. Therefore, an allograft was considered.

A review of the literature revealed a variety of traditional laboratory animal species used for research and refinement of human tendon graft procedures.[3,18,31,39] Nonhuman primates have been used as research models for experimental allografts,[8,40] however, to our knowledge, a tendon allograft has never been performed in laboratory animal species as a component of clinical care. In human clinical practice, it is common to either freeze-dry or fresh-freeze donor tendon allografts.[32] As mentioned previously, these procedures diminish the antigenicity of grafts via decellularization to reduce the chance of graft rejection yet allow for storage and use at a later time. However, the freezing process may alter graft biomechanical properties and tensile strength and could contribute to long-term failures.[9,12,19,37,38,44] In the clinical case we present here, because both animals were of conventional viral status, there was minimal concern about viral disease transmission. In addition, because the relative antigenicity of tendon is low, compared with other tissues, due to its low cellularity[14] and minimal vascularization, no treatment of the donor tendon was performed.[14,23,24] Furthermore, because a fresh-tissue donor was available at the time of tissue transplantation, no long-term storage of the graft was required. For these reasons, the donor tendon was harvested and transplanted as fresh tissue and did not undergo a freezing process.

Our surgical approach mimicked those performed in humans with the exception of tacking of the tendon to the surrounding tissues. This additional stabilization contributed to inhibition of sliding movement of the engrafted tendon and may have caused adhesions along its length, which are considered undesirable in human medicine. Although this sequelae was of concern, our primary intent was to provide a scaffolding basis for the migration and growth of the recipient's cells. Our macaque's recovery did not appear to be hampered, and, in fact, was much faster than the 6 to 12 wk time frame generally recommended for humans. In addition, a follow-up exam performed approximately 10 mo after surgery revealed that the repaired limb was stable and demonstrated signs of adequate use and range of motion similar to that of the unaffected limb.

The allograft used in this case provided a means of calcaneal tendon repair that, even with the challenges of postoperative wound complications, resulted in full function of the leg within 6 wk. If this technique is to be used in a clinical setting, we recommend harvesting the maximal amount of calcaneal tendon and posterior tuberosity of the calcaneus bone to facilitate tissue manipulation and insertion of the allograft. Additional consideration of immunogenicity via decellularization of the allograft by using methods such as freezing may be advisable to further ensure transplant success. In our case, utilization of this surgical technique appeared to provide a rapid healing time, did not cause negative sequelae of scar formation with reduction of limb use, and avoided the possible rejection of a synthetic or xenograft alternative. Allograft replacement of the avulsed or necrotic calcaneal tendon should be considered as a viable alternative to euthanasia of delayed secondary healing in rhesus macaques.

Acknowledgments

We thank the skilled veterinary technicians at the CNPRC for their efforts in helping manage this clinical case. Most notably, we acknowledge Ms Sue Sussdorf-Vigil for initiating the research into this surgical technique. We also thank Mr Mark Allen for his photo assistance.

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