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Case Report

Efficacy of Antibiotic-Impregnated Polymethylmethacrylate Beads in a Rhesus Macaque (*Macaca mulatta*) with Osteomyelitis

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Here we describe the successful surgical implementation of antibiotic-impregnated polymethylmethacrylate beads in a rhesus macaque (*Macaca mulatta*) with marked osteomyelitis. The macaque presented to the veterinary clinic with grossly contaminated bite wounds in the left ankle secondary to conspecific trauma. Radiographic findings were highly suggestive of osteomyelitis. Additional differential diagnoses included bony infarct, fracture, and cellulitis. In light of the location of the lesion and extensive tissue trauma, the animal had a poor prognosis. Systemic, broad-spectrum antibiotics were instituted. After 2 wk of care, lesions did not respond to empirical therapies. On consultation, a veterinary orthopedic surgeon at another facility recommended placement of antibiotic-impregnated polymethylmethacrylate beads at the sites of osteomyelitis. The animal underwent minor surgery in which beads were introduced into the wound. The monkey had a positive response to therapy. The animal regained full function and was returned to outdoor social housing. Veterinarians are encouraged to consider using antibiotic-impregnated polymethylmethacrylate beads when treating osteomyelitis in other nonhuman primates and in other traditional laboratory animal species.

Rhesus macaques can be aggressive, and mild to marked trauma can result from agonistic social encounters.[6] The AAALAC-accredited California National Primate Research Center houses more than 4000 rhesus macaques (*Macaca mulatta*) in large outdoor social corrals. The incidence of animals presenting to the center's veterinary hospital with traumas requiring sutures or amputation of digits ranges from 5% to 9% annually. Bite wounds predominate and frequently involve extremities (tail tips and digits). Open wounds place animals at risk for development of acute or chronic infections, including osteomyelitis.[8,9,11,21] Bacterial contaminants reflect the presence of oral flora secondary to characteristic wounding (for example, *Bacteroides* spp., coagulase-positive *Staphlococcus* spp., and *Eicinella* spp.).

Clinical management of osteomyelitis is challenging. The standard of care is based on irrigation of the wound, debridement of necrotic tissues, and administration of systemic antibiotics. Efficacy of systemic antibiotic therapy can be compromised due to poor tissue perfusion and compromised vasculature. Regimens for local administration of antibiotics are being developed continually to improve orthopedic wound management.[5,8,9,11,19,21,24,26] Antibiotic-impregnated polymethylmethacrylate (bone cement) is used in human and veterinary orthopedic surgery to provide high, localized concentrations of antibiotics in high-risk, poorly vascularized wounds.

Few cases of osteomyelitis have been reported in nonhuman primates, and even fewer reports reflect successful management of such conditions.[4,23,25,27,28] Here we document the successful clinical use of antibiotic-impregnated polymethylmethacrylate beads to treat osteomyelitis in a laboratory-housed rhesus macaque.

Case Report

Case presentation. July 2008, a 5.5-y-old, captive-born, mother-reared rhesus macaque (*Macaca mulatta*) presented to the veterinary hospital at our facility. This 9.87-kg adult male was socially housed with more than 100 other conspecifics in a large, outdoor, half-acre corral and was assigned to the facility's breeding colony protocol. Clinical care was performed in accordance with policies approved by the IACUC at the University of California, Davis. On the day of presentation, animal care staff reported that the monkey demonstrated an altered gait with poor weight-bearing noted on the left pelvic limb. A grade 4/5 lameness was observed.[1]

Physical exam revealed a laceration on the dorsomedial surface of the left heel, consistent with a puncture wound secondary to bite trauma. A fistula was visible, and purulent material was expressed from the lesion. Initial radiographic findings revealed marked osteolysis of the left calcaneus, with multiple bony fragments and moderate soft tissue swelling. The common calcaneal tendon was thickened. Differential diagnoses included osteomyelitis (bacterial or fungal etiology), fracture, and cellulitis (Figure 1). Marked osteomyelitis of the left calcaneus with a concurrent

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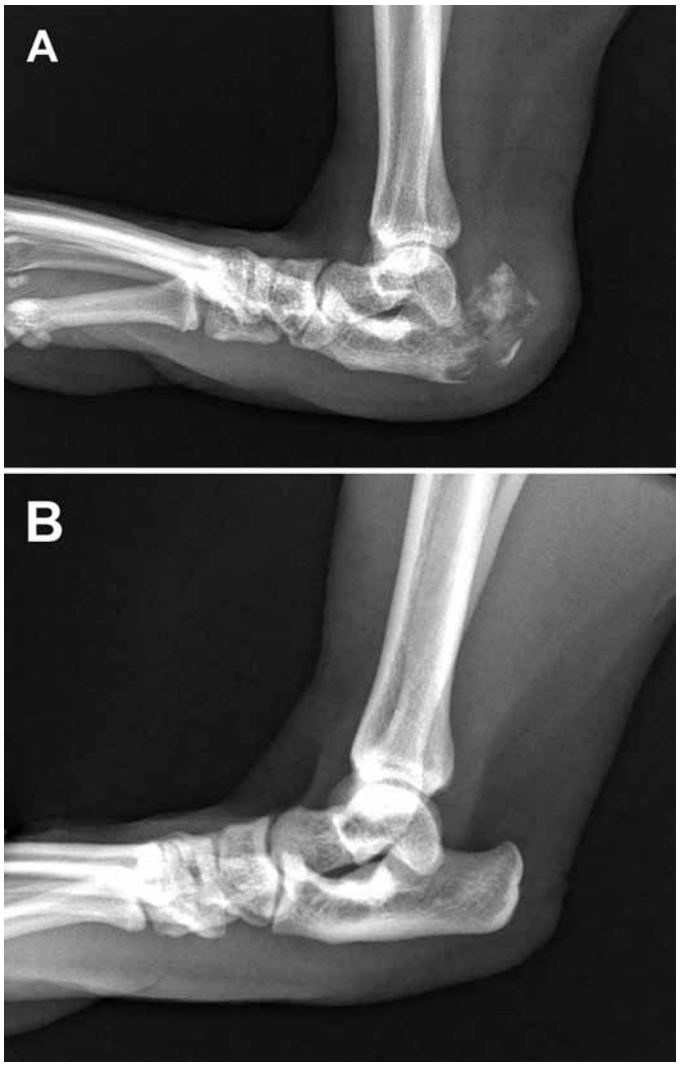

Figure 1. Radiographs taken at initial presentation. (A) Abnormal left ankle. (B) Normal right ankle. There is osteolysis of the left calcaneus with multiple fragments, moderate soft tissue swelling, and thickening of the common calcanean tendon.

fracture or sequestrum was established as the working diagnosis. A bacterial etiology was presumed because of the obvious bite wound. Because of the lesion's location and anticipated compromise to the left common calcaneal tendon, the animal had a grave to poor prognosis. The animal was admitted to the veterinary hospital and housed individually in a species-specific indoor monkey cage.[2,13,17]

Wound management. Empirical therapy was instituted and involved regular lavage of the wound with dilute chlorhexidine solution (Nolvalsan, Fort Dodge, Fort Dodge, IA) every 24 to 48 h for 6 d, bandaging for 4 wk, and systemic administration of clindamycin (12.50 mg/kg PO every 8 h for 4 wk; clindamycin phosphate, Hospira, Lake Forest, IL), cefazolin (25.0 mg/kg IM every 12 h for 6 d; Steri-Pharma, Syracuse, NY), and ketoprofen (2.0 mg/kg IM once daily for 4 d; Ketophen, Fort Dodge Animal Health). Surgical exploration of the wound 5 d after presentation failed to recover the radiographically appreciated fragments. The animal was sedated by using ketamine (5.0 to 30.0 mg/kg IM; Ketathesia, Butler Schein Animal Health Supply, Dublin, OH) with or without dexmedetomidine (15.0 µg/kg IM; Dexdomitor, Pfizer Animal Health; New York, NY) as needed for wound lavage, bandage changes, and surgical exploration. Ibuprofen (9.0 mg/kg PO daily for 4 d; Children's Motrin, McNeil Consumer Healthcare, Fort Washington, PA) was given for postsurgical analgesia.

Purulent discharge and marked lameness persisted. Animal compliance was poor for oral antibiotic treatment. Oral therapy was discontinued and changed to intramuscular therapy (12.5 mg/kg IM clindamycin every 8 h for 7 d). Although extensive attempts were made to transition the animal back to systemic oral medication, poor compliance persisted. Palliative wound care continued. Within a week of hospital care, the muscles of the left leg had atrophied considerably. The radiographic appearance of the calcaneus had not changed since presentation. The fistula resolved after 12 d of wound management. At this point, a veterinary orthopedic surgeon at another institution recommended surgical implantation of antibiotic-impregnated polymethylmethacrylate beads at the site of infection to provide high antibiotic concentrations directly at the site of osteomyelitis.

Surgical implantation of antibiotic-impregnated polymethylmethacrylate beads. On day 20 after presentation, polymethylmethacrylate beads impregnated with vancomycin and tobramycin were surgically implanted at the site of osteomyelitis (Figure 2). The macaque was anesthetized routinely with ketamine (10.0 mg/kg IM) for premedication followed by 1.5% to 2% isoflurane (Hospira) for inhalational maintenance. A 2-cm skin incision was made lateral to the calcaneal tendon of the left ankle. Muscle bellies were separated by blunt dissection, and a pocket was created between the tibia and calcaneus. Sterile antibiotic-impregnated polymethylmethacrylate beads (n = 10; diameter, 1 to 3 mm) were surgically introduced into the pocket. To maximize antibiotic administration, beads were packed into the pocket until closure appeared compromised. The antibiotic doses at the site of active infection were estimated to be 60 to 120 mg tobramycin and 50 to 100 mg vancomycin; the actual dose eluted was recognized to reflect bead size, bead shape, and tissue vascularization. Each of the doses provided to the animal was calculated to be less than 10 times a comparable single systemic dose of these same antibiotics (9.87 kg; 2 mg/kg tobramycin = 19.74 mg tobramycin [therefore approximately 6 times the calculated systemic dose was provided in the beads]); 15 mg/kg vancomycin = 148.05 mg [therefore approximately the calculated systemic dose was provided]). Muscle bellies were closed with simple interrupted sutures of 4-0 polydioxanone (PDS II suture, Ethicon, Somerville, NJ). Subcutaneous tissue was closed in a continuous running pattern of 4-0 polydioxanone. Skin edges were apposed with simple interrupted sutures of 3-0 polyglactin 910 (coated Vicryl suture, Ethicon). A Robert–Jones bandage was placed on the left leg. The animal received ketoprofen (2.0 mg/kg daily for 6 d) and buprenorphine (0.03 mg/kg every 8 h for 3 d; Buprenex, Reckitt Benckiser Healthcare, Hull, UK) for postoperative pain management.

Postoperative care. The Robert–Jones bandage was removed the day after surgery. Mild soft tissue swelling was evident surrounding the surgical incision. Mild to moderate pressure sores were developing on the medial and plantar surfaces of the left ankle. Marked disuse muscle atrophy was palpated. Decreased range of motion was appreciated on flexion and extension was com-

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Material	Amount	Directions
Tobramycin (tobramycin powder; X-Gen, Big Flats, NY)	3 vials (1.2 g base per vial)	Stir dry powders together in a sterile disposable vacuum bowl.
Vancomycin (vancomycin powder; Novaplus, Lake Forest, IL)	2 vials (1 g base per vial)	Stir dry powders together in a sterile vacuum bowl.
Polymethylmethacrylate polymer (Stryker Surgical Simplex P; Howmedica Osteonics, Mahwah, NY)	1 package (40 g per package)	Stir dry powders together in a sterile vacuum bowl.
Methylmethacrylate monomer (Stryker Surgical Simplex P; Howmedica Osteonics, Mahwah, NY)	1 vial (20 mL per vial)	Add to blended dry powders and mix into dough by using a spatula.
Mixed dough	—	Rapidly roll dough into beads of various sizes or place mixture in a syringe and expel small amounts to roll into beads.
Beads	~100 beads (diameter, 1–3 mm)	Allow beads to air-dry. After hardening, place into sterile containers for surgery or to save for future surgery.

Figure 2. Protocol used to make antibiotic-impregnated polymethylmethacrylate beads was based on information provided in references 5 and 24. Sterile technique is to be maintained throughout the manufacturing process. Estimated yield is 100 beads (diameter, 1 to 3 mm).

promised markedly in the left knee and ankle joints. Sustained passive range-of-motion physical therapy and deep muscle massage were performed, and the Robert–Jones bandage was replaced.

On day 3, the bandage again was removed. The skin incision was healing by primary intention. Soft-tissue swelling around the ankle had resolved almost completely. The animal was given sustained passive range-of-motion physical therapy and deep muscle massage beginning on day 3 and repeated every other day until 18 d after surgery. On day 12 after surgery, the animal was allowed to spend 3 h in an exercise pen, where he was observed weight-bearing on all 4 legs and voluntarily demonstrated jumping, climbing, walking, and running movements. There was a grade 4/5 lameness with a pronounced hip-hike, reflecting abduction of the left leg.[1] The day after the macaque's exposure to the exercise pen, a pronounced 1.0 cm × 1.5 cm thickening was palpated in the calcaneal tendon proximal to the surgical incision. Differential diagnoses included localization of fibrous tissue, focal muscle avulsion, or polymethylmethacrylate bead migration. This thickening increased in density and then slowly resolved during the course of physical therapy. The animal continued to receive 3 to 6 h of exposure to the exercise pen every other day for 2 wk.

On day 19 after surgery, mobility was markedly improved, with evidence of a grade 1/5 lameness.[1] Radiographs obtained 20 d after surgery showed new bone joining the fragments of the calcaneus in a smooth, regular appearance, and soft tissue swelling was decreased. The radiopaque, implanted beads had not migrated from the implantation site (Figure 3). The macaque was discharged from the hospital to indoor social housing 60 d after presentation.

Follow-up care. Two years after the injury, the macaque was returned to outdoor social housing. Currently, the animal is an alpha male of a small outdoor colony of socially housed rhesus macaques. A smooth, undulating cortex on the plantar surface of the left calcaneus can be appreciated, and previous fragments have become incorporated into the calcaneus with development of a normal trabecular pattern. The insertion of the common calcaneal tendon is mildly thickened. Soft tissues and musculature appear to be within normal limits. No persistent lameness can be appreciated. On deep palpation, only a very mild thickening of the left ankle joint, consistent with the continued presence of the implanted polymethylmethacrylate beads, can be discerned (Figure 4). Fibrous tissues surrounding the beads are believed to support stabilization of the tarsus. The animal will be assessed for removal of the beads should secondary complications develop (for example, development of lameness or sterile abscess). No thickening of the calcaneal tendon could be palpated. The macaque's CD4:CD8 ratio, clinical chemistry profile, hemogram, and leukogram were all within normal limits as compared with colony-specific standards. No residual antibiotic could be detected systemically (plasma vancomycin concentration, less than 2.0 mg/L).

Discussion

In the late 1960s, a West German physician introduced the concept of local antibacterial application to minimize undesirable effects associated with traditional systemic therapies. Specifically, the physician designed a form of antibiotic-impregnated bone cement and used this product to treat infected arthroplasties. The original technique involved placement of antibiotic-impregnated bone cement into the bone cavity and was highly successful.[9-11] However, the bulky cement inhibited drainage of secretions from the debridement foci and proved prohibitively difficult to remove when redebridement was necessary. A second West German physician built on the original technique and developed antibiotic-impregnated cement beads.[9-11] The beads were molded along a steel surgical wire and were impregnated with gentamicin. This alternative technique provided a flexible and easily removable therapeutic modality for local antibiotic therapy. Due to the minimized risk of nephrotoxicity, ototoxicity, and allergic responses, prophylactic and therapeutic applications of this modality quickly became common in both human and veterinary orthopedic medicine and surgery.[5,7,9-11,18,19,21]

From the late 1960s until the early 2000s, in vitro and in vivo experiments were performed to quantify effects of this novel therapeutic modality. For example, in 1998, antibiotic-impregnated polymethylmethacrylate beads were used to treat experi-

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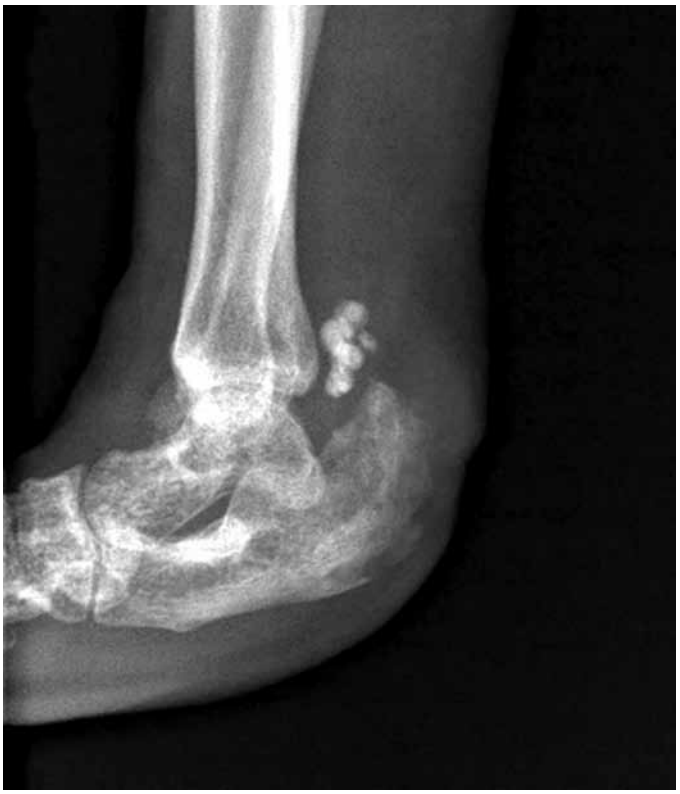

Figure 3. Radiograph taken 20 d after presentation and implantation of antibiotic-impregnated polymethylmethacrylate beads. New bone is seen joining the fragments of the calcaneus, with a smooth, regular appearance and reduced soft tissue swelling. Radiopaque implanted beads have not moved noticeably from the original site.

mentally induced thoracis in a guinea pig empyema model.[14] In 2002, the effects of a calcium hydroxyapatite antibiotic implant in a localized osteomyelitis rabbit model was evaluated,[22] and in 2005, gentamicin-impregnated polymethylmethacrylate beads were compared with gentamicin-impregnated collagen sponges in a rat model of osteomyelitis.[16] Human clinical reports reflect regular application of this now-standard antibiotic administration technique.[15,26] Equine and canine veterinary clinical trials reflect similar applications and successes to human literature.[20] However, no previous literature reports the clinical application of this therapeutic procedure in nonhuman primates or other laboratory animals.

Laboratory animal veterinarians must carefully consider the clinical use of antibiotic-impregnated polymethylmethacrylate beads before their application. Specific concerns might include compromise of research models, particularly those used to evaluate innate and humoral immune responses. The vehicle traditionally used for local administration of antibiotic is methylmethacrylate bone cement. Laboratory data support that in vivo introduction of polymethylmethacrylate does not affect IgG, IgM, or IgA immunoglobulins.[11] In contrast, the implantation of polymethylmethacrylate can transiently alter various bacterial inhibiting factors, peripheral lymphocytes, late-acting components of the complement sequence, and the bacterial capability of polymorphonuclear leukocytes.[11] Regardless, these changes normalize over time and are unlikely to be of significant concern with respect to long-lived research subjects.[11]

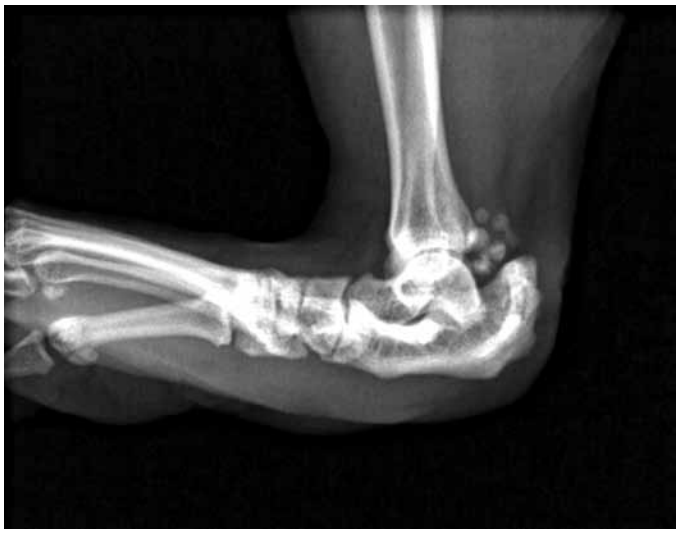

Figure 4. Radiograph taken 2 y after presentation. There is a smooth, undulating cortex on the planar surface of the left calcaneus. The fragments have been incorporated into the calcaneus with a normal trabecular pattern. The insertion of the common calcaneal tendon is mildly thickened. Radiodense beads persist without noteworthy migration from original site of implantation. Soft tissues and musculature appear to be within normal limits.

Approximately 5% of the impregnated antibiotic is released in vivo during the first 24 h after bead implantation; thereafter the elution rate progressively diminishes over weeks to months. The pattern of antibiotic release over time reflects unique properties of the selected antibiotic, incorporated antibiotic concentration, and unique biochemical properties of the vehicle.[3,5,9,11,12,18,21,24,26] When using a nonabsorbable vehicle (for example, polymethylmethacrylate), surgeons must address the issue of bead removal. In human medicine, surgeons often remove the beads during a subsequent surgical procedure. Faced with species-related challenges, veterinary surgeons may elect to leave the beads in place. Factors that may influence this decision can include financial constraints, implant stability, animal use (for example, food, fiber), species lifespan, and owner and animal compliance. The persistent presence of polymethylmethacrylate in vivo can promote the development of local antibiotic resistance.[8,21,26] The clinical effect and relevance of such resistance have yet to be quantified.

Antibiotic-impregnated bioresorbable materials have been developed. Calcium sulfate is one such material that has been used clinically in veterinary medicine. The clinical success of antibiotic-impregnated calcium sulfate parallels the use of antibiotic-impregnated polymethylmethacrylate beads. Prepackaged, standardized, medical-grade antibiotic-impregnated calcium sulfate beads have recently become commercially available in the United States.[8] Among commercial resorbable products, the choice of antibiotics is limited, and the bead size available may not be appropriate for all wounds and species. Medical-grade, antibiotic-impregnated polymethylmethacrylate beads are not available commercially in the United States. Antibiotic choice is limitless for nonresorbable products and is restricted only by the need to select materials that can tolerate the exothermic reaction produced during creation of the beads (Figure 2). Bead size can be modified to accommodate individual wounds and animals. Professional discretion is needed to select the most appropriate

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therapy for a particular animal. The application of either absorbable or nonabsorbable antibiotic-impregnated substrate likely will support positive wound healing in veterinary patients.

In conclusion, the surgical introduction of antibiotic-impregnated polymethylmethacrylate beads in the macaque we present proved highly successful. The animal completely regained limb function and was able to return to outdoor social housing. No quantifiable measures suggested compromise to the animal. Readers are encouraged to consider antibiotic-impregnated beads when treating osteomyelitis in nonhuman primates and other laboratory animal species.

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