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One-Stage Treatment of Chronic Calcaneal Osteomyelitis with Bone Morphogenetic Protein 2 and Local Antibiotic Delivery in a Cat

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Abstract : An age-unknown, 4.8 kg, male, wild, domestic short-hair cat was presented for left hindlimb lameness. A physical examination revealed a draining tract which was suspected of bite on left calcaneal bone. The left tarsal joint was markedly swollen and exudates were observed around the draining tract. Sequestrum at left calcaneus bone, and osteolysis were identified by radiography. The sequestrum and its surrounding exudative tissue were debrided during surgery and the tissue was submitted for bacterial culture and sensitivity test. The debridement caused a bone defect (1.5 cm × 0.5 cm × 0.5 cm) on the medial left calcaneal bone. Plate and screw fixation was performed to the calcaneus bone as buttress plate. Recombinant human bone morphogenetic protein-2 (rhBMP-2) loaded hydroxyapatite was implanted in the bone defect. Furthermore, Amikacin-impregnated collagen sponges were also placed around bone plate to deliver local antibiotics. A systemic antibiotic treatment regimen based on bacterial culture and sensitivity test results was administered for 4 weeks. The wound properly healed without any signs of infection, and the bone healing was confirmed by radiography. The patient showed normal weight bearing ambulation at 18 weeks after surgery. The use of rhBMP-2 and local antibiotic delivery system is a good surgical option for the one-stage treatment of chronic osteomyelitis.

Key words **:** rhBMP-2, local antibiotic delivery system, chronic osteomyelitis, one-stage revisioin.

Introduction

Osteomyelitis is an infectious disease of bones accompanied with inflammatory process caused by infectious microorganism, mainly bacteria (4). Osteomyelitis has been traditionally classified as either hematogenous or posttraumatic based on its origin and as acute or chronic in accordance with the duration since disease onset (4,19). The most common form of bone infection seen in small animal practice is chronic posttraumatic osteomyelitis. This infection can be caused by trauma, surgical procedures such as internal fixation for fracture, or joint prosthesis.

Osteomyelitis doesn't occur from infection only, but rather it occurs when ischemic condition of bone and its adjacent tissue with concurrent bacterial colonization. During the acute phase of osteomyelitis, the bacteria inoculated into ischemic area cause an acute inflammatory response that results in tissue necrosis and the formation of exudates. The affected animals develop localized swelling, pain and systemic illness such as fever, loss of appetite, and lethargy. The exudates will increase without proper treatment and can induce localized vascular compromise and subsequent tissue ischemia that cause bone necrosis.

Chronic osteomyelitis develops within several months after acute osteomyelitis has subsided (4,15). The clinical signs include lameness, pain, and a draining sinus tract. Chronic osteomyelitis is also characterized by a sequestrum and its surrounding zone, called the involucrum, in radiographs (4,15).

The treatment of chronic osteomyelitis is challenging. The lack of blood supply to the area impairs the host immune system and the systemic delivery of antibiotics to the affected site (17). Thus, chronic osteomyelitis is one of the most disastrous orthopedic conditions for patients, pet's owners, and veterinary orthopedic surgeons (6). Chronic osteomyelitis requires rapid diagnosis and aggressive treatment because of the difficulty associated with complete disease eradication.

The traditional treatment for chronic osteomyelitis involves multiple-stage revision that are often two-stage treatments. This approach is considered the gold standard for treating osteomyelitis (9,14). Surgical treatment is performed in separate stages, and the goal of the initial stage of surgical intervention is to remove or disrupt the infected tissue. The surgery may involve various treatments, including lavage, radical debridement, removal of preexisting implants if present and dead space management. The identification of the infectious agent is essential for adequate antibiotic therapy. The medical treatment should be administered for at least 4 to 6 weeks. Once the infection arrest is assessed, next surgical

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stage is indicated. The purpose of another stage of the surgical intervention is to restore bone stability and enhance the healing of the bone fracture or any bony defect caused by debridement.

The two-stage revision has many limitations, though it is considered a gold standard of treatment for chronic osteomyelitis. First, the patients require two surgeries, which increases the risk of morbidity, extends the hospitalization period, and increases costs. There are also technical limitations associated with two-stage revision, that is the management of large bone defect and bone stabilization when sequestrum is extensively removed.

However, in human medicine, alternative treatment has been introduced in certain case (11,12); the one-stage revision. The one-stage treatment can be accomplished by using a combination of thorough debridement of contaminated tissue, bone stabilization, and then placement of a degradable antibiotic delivery system. To author's best knowledge, treatments for chronic osteomyelitis using a one-stage revision are rarely reported in small animal practices.

The purpose of this case report is to describe a one-stage revision method and the clinical outcome of a cat with chronic osteomyelitis with sequestrum formation.

Case

A 4.8 kg, male, wild, dometstic short-hair cat of unknown age was presented with left hindlimb lameness. The cat had a history of drainage treatment and antibiotic therapy for suspected osteomyelitis of the left leg at a local animal hospital for 5 days and exhibited non-weight bearing lameness. A Physical examination revealed a draining tract caused by a suspected bite on the left calcaneus. The left tarsal joint was markedly swollen, and a bite wound with adherent yellow exudates was observed around the calcaneal region. A draining tract caused by the bite wound was identified.

The radiographic examination (Fig 1) revealed sequestrum formation (1.1 cm × 0.4 cm) with surrounding involucrum in the left calcaneus and concomitant soft tissue swelling. The diagnosis was chronic osteomyelitis with sequestrum formation on the left calcaneus bone. The surgical exploration on the left calcaneus was performed under general anesthesia.

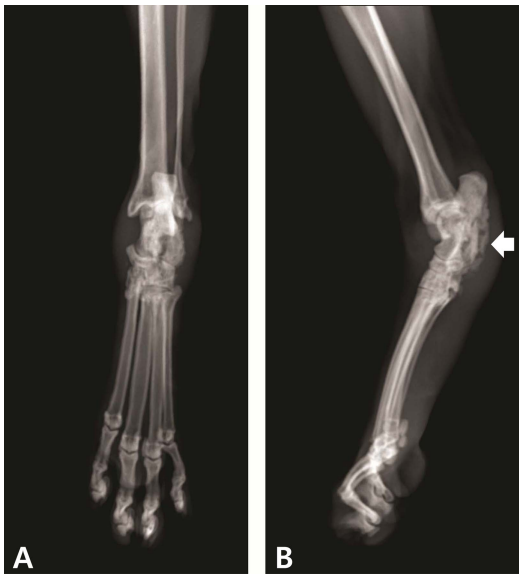

Fig 1. Orthogonal view radiographs of the left calcaneus. Sequestrum (arrow) is well obsereved as a localized opacity surrounded by radiolucent involucrum on the lateral view.

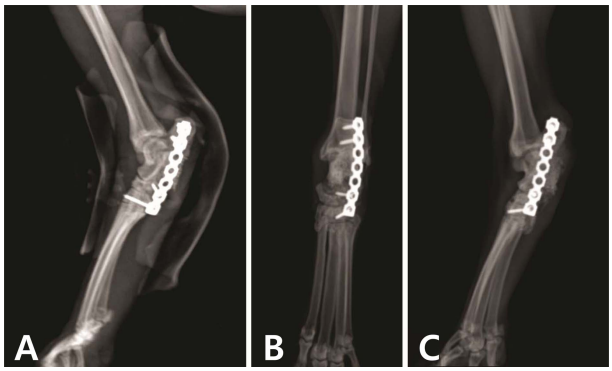

Fig 3. Postoperative radiographs showing callus formation. There was no evidence of implant failure 5 weeks after surgery. The mediolateral view of left calcaneus after surgery (A), The anterioposterior view 5 weeks after surgery (B), and the mediolateral view 5 weeks after surgery (C).

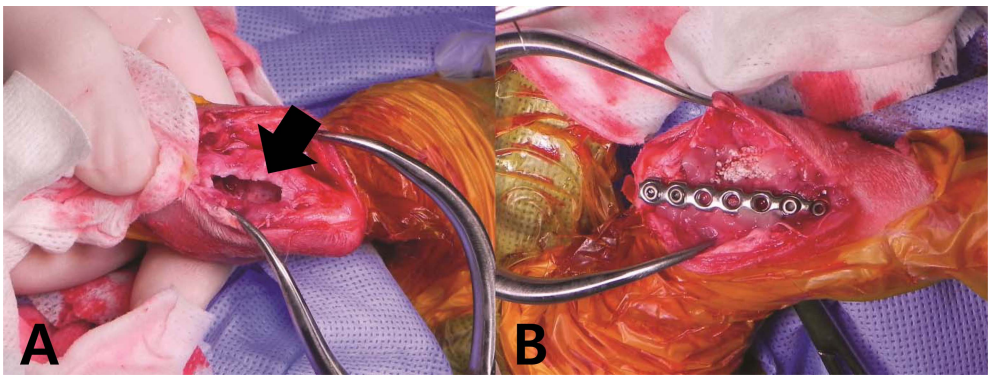

Fig 2. Intraoperative photograph of the calcaneus. Note the large bone defect (black arrow) which occupied approximately 70% of calcaneal bone following aggressive debridement (A). Intraoperative photograph of the large defect bridged by plate and filled with hydroxyapatite containing rhBMP-2. There were antibiotic impregnated collagen sponges were placed around the plate and adjacent tissue (B).

After premedication with diazepam (0.5 mg/kg IV, Merod®, Donghwa Co, Seoul, Korea) and butorphanol (0.2 mg/kg IV, Butorphan®, Myoungmun Pharmaceutical Co, Korea), anesthesia was induced with propofol (6 mg/kg IV, titrate to effect, Provive 1%®, Claris Lifesciences Ltd., India) and maintained with isoflurane (Ifran®, Hana Pharm. Co., Ltd., Korea). The animal also received epidural anesthesia consisting of 0.5% bupivacaine (0.5 mg/kg, Bupivacaine HCl 0.5%, Myungmoon Pharm. Co., Korea). The patient was positioned in right lateral recumbency for surgery. A lateral approach was used to expose the the left calcaneus. The examination of the calcaneus revealed a 1-cm-long sequestrum and surrounding involucrum. Sequestrectomy and meticulous debridement was conducted using a rotating burr until bleeding occurred from the bone. The aggressive debridement created a defect measuring 1.5 cm × 0.5 cm × 0.5 cm on the medial aspect. This bone defect occupied approximately 70% of the calcaneus (Fig 2A). The debrided sequestrum and its surrounding tissue were submitted for bacterial culture and sensitivity test. The remaining calcaneus was stabilized using internal fixation with a plate and screws to prevent an avulsion fracture.

Hydroxyapatite (0.25 g) containing Bone Morphogenetic Protein 2 (rhBMP-2, 0.25 mg/ml, Anibog®, Daewoong CGBIO. Co, Korea) was placed in the bone defect to enhance bone healing. Amikacin-impregnated collagen sponges were also placed around bone plate to deliver local antibiotics and prevent the formation of biofilm on the surface of metal implant (Fig 2B).

The patient recovered from anesthesia without any complication and tramadol (2 mg/kg IV, BID, Tramadol HCl®, Huons, Korea) was administered for postoperative pain management. An antibiotic therapy with enrofloxacin (5 mg/kg PO, SID, Baytril®, Bayer, USA) and amoxicillin/clavulanate potassium (20 mg/kg PO, BID, Clavamox®, Pfizer, USA) was initiated from post-operative day 9 for 4 weeks. The antibiotics were selected based on the bacterial culture and sensitivity test results.

The wound healed normally without any signs of infection. There were no complications of implant failure or loosening, and the bone healing was confirmed by radiography (Fig 3). The patient showed normal weight bearing ambulation at the last follow-up, 18 weeks postoperatively.

Discussion

The two-stage revision is considered the gold standard for treating chronic osteomyelitis (9,14), and there is a concern regarding a higher re-infection rate of one-stage revision. However, There are successful outcome of one-stage revision in human medicine, and this approach has been reported routinely (9,12) and in selected cases (9,12) due to the obvious advantages of one-stage revision. The advantages of a one-stage surgery include avoiding potential morbidity from a second procedure, less discomfort from surgery, a shorter recovery period, and financial savings (5,9,11). In this case, a successful surgical prognosis was achieved by a one-stage treatment of chronic osteomyelitis with a sequestrum. The advantages of the one-stage revision were clear because the patient was a cat, and these animals are prone to stress and discomfort following surgery and postoperative care.

A One-stage revision was the selected method of treatment for chronic osteomyelitis in this case. Before surgery, large bony defect due to aggressive debridement for sequestrum was anticipated and consequent tension fracture in the defected calcaneus was concerned. Therefore, we restored the bone defect and stabilized the calcaneus using a one-stage procedure.

There is still active debate regarding the relative merits of one-stage or two-stage techniques. A recent study reported that the success rates and re-infection rates were better for two-stage revisions than one-stage revisions (21) (Wolf *et al*. 71.9% vs 78.2% and 12.3% vs 6.5%, one-stage revision and two-stage revision respectively). However, the majority of comparative studies compare two cohorts with different selection criteria. These differences make any relevant comparison impossible (9).

In this case, local antibiotic delivery system was utilized to reduce the possibility of re-infection. Furthermore, systemic antibiotics were administered on the basis of bacterial culture and sensitivity test. However, systemic antibiotics may have limited action in the affected site due to poor blood supply, prolonged antibiotic regimes, or presence of biofilm (17). There are several advantages of local antibiotic implants for treating osteomyelitis (3,7). A high local antibiotic concentration can be maintained at surgical site, and the drugs are effective, despite the presence of biofilm and ischemic condition. Additionally, it can kill bacteria that is resistant to antibiotic sensitivity. The local antibiotic delivery system also reduces bacterial mutation and minimizes systemic side effects, despite high concentrations in the localized lesion. Various materials can be used as antibiotic elution media (3,7). However, prior studies have revealed that bacteria can adhere and colonize antibiotic impregnated implants. Biodegradable materials such as collagen can elute proper amounts of antibiotics over 7-14 days in vivo (1). In one human study, the treatment of chronic osteomyelitis with a local antibiotic delivery system showed better outcomes than did treatment without a local antibiotic delivery system (8). Thus, a local antibiotic delivery system is preferred for the treatment of localized osteomyelitis lesions. The patient did not display any signs of re-infection or complications related to local antibiotic delivery system.

In the above described case, a commercial rhBMP-2 (0.25 mg/ml) with hydroxyapatite (0.25 g) carrier is used to enhance bone regeneration of the defect (20) caused by aggressive debridement. The advantage of rhBMP compared to an autologous bone graft include the readily available supply, no additional personnel to harvest graft, short anesthetic time, and low donor site morbidity (10,13). Bone grafts are contraindicated when there are clinical signs of infection observed. However, there is no guaranteed time established for indication of bone graft after eradicating infection (12). It is also difficult to confirm the infection is actually eradicated or arrested. In this case, to control infection, combination of meticulous debridement and copious lavage was performed in addition to the use of local antibiotic delivery system. The patient did not display any clinical signs of infection, and

bone regeneration was identified.

The optimal quantity of rhBMP needed for proper bone regeneration has not been established. There are various commercial products and carriers available. In a recent report (10), 4 dogs that had delayed or nonunion of bone fractures, osteotomies, or arthrodeses were treated with application of rhBMP-2 (0.2 to 1.6 mg) using either a calcium phosphate matrix or absorbable collagen sponge carrier. There were rapid radiographic signs of union detected in all dogs, and the patients had excellent outcomes. In another reports, 4 dogs that had reconstruction after segmental mandibulectomy were treated with a uniform dose of 0.5 mg/ml with a 50% soak volume and then the defects were well integrated to the adjacent native tissue (2,18). In this case, radiography imaging indicated the bone regeneration with hydroxyapatite-containing rhBMP-2 placed in the bone defect caused by debridement.

Conclusion

A successful short-term clinical result was obtained in this case using a one-stage treatment despite the presence of a large defect caused by sequestrum formation. For one-stage treatment of chronic osteomyelitis, aggressive debridement is required to remove sequestrum, and biodegradable local antibiotic delivery system and rhBMP-2 can be a good surgical option for bone defect caused by chronic osteomyelitis.

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