Case report

Bone stock reconstruction for huge bone loss using allograft-bones, bone marrow, and teriparatide in an infected total knee arthroplasty[☆]

Masataka Nishikawa^{a,*}, Shoichi Kaneshiro^c, Kenji Takami^a, Hajime Owaki^{a,b}, Takeshi Fuji^a

^a Department of Orthopaedic Surgery, Japan Community Healthcare Organization Osaka Hospital, 4-2-78 Fukushima, Fukushima-ku, Osaka 553-0003, Japan

^b Department of Rheumatology, Japan Community Healthcare Organization Osaka Hospital, 4-2-78 Fukushima, Fukushima-ku, Osaka 553-0003, Japan

^c Department of Orthopaedic Surgery, Osaka Rosai Hospital, 1179-3 Nagasone-cho, Kita-ku, Sakai, 591-8025, Japan

ARTICLE INFO

Article history:

Received 22 December 2017

Received in revised form 1 March 2018

Accepted 8 March 2018

Available online 8 March 2018

Keywords:

Allograft-bone

Bone marrow

Rheumatoid arthritis

Teriparatide

ABSTRACT

Bone stock reconstruction using allograft-bones, bone marrow (BM), and teriparatide (TPTD) is reported. Huge and extensive bone losses occurred in the medullary cavity of the femur and tibia of a 55-year-old female rheumatoid arthritis patient with severe osteoporosis after debridement of her infected total knee arthroplasty. Because of the risks of unstable prosthetic fixation and intra-operation fracture, we first reconstructed the bone stock. Chipped allograft bones mixed with BM were implanted in the bone defects, and TPTD was administered for the osteoporosis therapy. Good bone formation was found by computed tomography after 4 months. Bone turnover markers and bone mineral density (BMD) were increased at 6 months. We confirmed good bone formation at the re-implantation surgery. The newly formed bone harvested during the re-implantation surgery showed active osteoblast-like lining cells. TPTD is known to enhance allograft bone union, mesenchymal stem cell differentiation into osteoblasts, and BMD. This tissue engineering-based technique might be improved by the various effects of TPTD. This method without any laboratory cell culture might be a good option for bone stock reconstruction surgery in ordinary hospitals.

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1. Introduction

During revision surgery of an infected total knee arthroplasty (TKA) in rheumatoid arthritis (RA) patients with osteoporosis, huge and extensive bone loss is often encountered. Management of bone loss is important for achieving successful outcome of the revision surgery. A variety of methods exist for reconstructing bone defects, including cement, autograft-bone, allograft-bone, modular solid-metal wedges and blocks, and porous or trabecular metal bone-replacing augments. However, none of these options provide sufficient new bone in cases with huge and extensive bone loss.

This case report presents an RA patient with severe osteoporosis and huge and extensive bone loss of an infected TKA who was successfully treated with allograft-bones, bone marrow (BM), and teriparatide (TPTD).

2. Case report

A 55-year-old woman presenting with RA underwent a left TKA. Six years later (61-years), a sinus tract over the knee joint was found. However, it healed with oral garenoxacin mesilate hydrate treatment. *Methicillin-sensitive Staphylococcus aureus* (MSSA) was detected in the discharge. She refused debridement and prosthesis removal surgery because of no other symptoms. Similar episodes repeated a few times over 5 years, and osteolysis around the prosthesis progressed. Eleven years after the TKA (66-years), she agreed to the surgery because of the chronic sinus tract and prosthesis loosening (Fig. 1).

Her recent treatment regime was 5 mg/day of prednisolone, 6 mg/week of methotrexate, and 1.5 mg/day of tacrolimus for the last 5 years. Her preoperative RA was classified as Stage IV and Class III,¹ and her laboratory results were 9600 white blood cells/ μ L (neutrophils: 95%), 0.52 mg/dL, C-reactive protein, and 61.5 ng/mL matrix metalloproteinase-3.

After debridement, huge and extensive bone losses remained in the femur and tibia. Further, the cortical bone at these sites was very thin and fragile. Antibiotic cement (2 g of vancomycin and

[☆] This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author.

E-mail address: ni4kawa-ma@umin.ac.jp (M. Nishikawa).

Fig. 1. Loosened total knee prosthesis before implant removal surgery.

(a) Anteroposterior and (b) lateral view X-rays of the left knee. Infected total knee prosthesis (*Methicillin-sensitive Staphylococcus aureus* positive) was loosened because of 5 years conservative therapy.

480 mg gentamicin per 40g-batch of bone cement) were placed in the joint and medullary spaces as local treatments (Fig. 2). Linezolid (1200 mg/day) and rifampicin (450 mg/day) were administrated as systemic antibiotic therapy for the first 15 days, and daptomycin (350 mg/day) and rifampicin for the next 11 days. Next, sulfamethoxazole (1200 mg/day), trimethoprim (240 mg/day), and rifampicin were administrated for 79 days. The laboratory data normalized by 4 weeks and remained after suspension of the antibiotics. These all antibiotics were administrated for the treatment of the pathogenic bacterium of infected TKA (MSSA).

We had planned to re-implant the prosthesis after eradication of the infection was achieved. However, we concluded that stable fixation of the prosthesis using only cement would be impossible because of the huge, extensive bone loss, and osteoporosis. Therefore, we decided to reconstruct the bone stock first. Although we evaluated a variety of candidate materials to reconstruct the bone stock, we chose to use allograft-bones, and BM.

The bone stock reconstruction surgery was performed 6 months after the first surgery (66-years). The joint fluid and soft tissue culture tests obtained during the surgery were negative. Femoral heads from total hip arthroplasties under informed consent as a

Fig. 2. Huge and extensive bone losses after debridement and prosthesis removal.

(a) Intra-operation digital image of the distal femur. (b) Anteroposterior and (c) lateral view X-rays of the left knee. After tissue debridement, huge and extensive bone losses were left in the medullary cavities of the distal third of the femur and proximal third of the tibia. Moreover, the cortical bone at these sites was very thin and fragile. White arrows (a) show the huge and extensive bone losses in the distal femur. Antibiotic cement spacers and beads were placed in the joint and medullary spaces (b and c).

bone bank had been collected as the source for the allograft-bone. First, allograft-bone blocks were placed in the medullary cavity of the distal femur and proximal tibia as bone plugs. Next, a total 20 mL of BM was aspirated from 4 sites on the bilateral iliac crests. Other chipped allograft-bones mixed and loaded with BM (allograft-BM) were implanted in the cavities of the femoral and tibial bone defects (Fig. 3).

After implantation, alfacalcidol (1.0 µg/day), calcium L-aspartate (800 mg/day), and TPTD were administrated as the osteoporosis therapy. TPTD was given 20 µg/day for the first month, but was changed to 56.5 µg/week for the next 5 months because of an allergic rash. TPTD was administrated for total 12 months.

Isoform 5b of tartrate-resistant acid phosphate increased from 267 before surgery to 350mU/dL, undercarboxylated osteocalcin increased from 2.11 to 11.7 ng/mL, and intact procollagen type I amino-terminal propeptide increased from 33 to 87.8 µg/L after 6 months. Bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (Discovery A; Hologic, Inc., Bedford, MA) increased by 3.8% (0.685 to 0.711 g/cm²) in the lumbar spine, by 9.8% (0.389 to 0.427 g/cm²) in the femoral neck, and by 15.0% (0.233 to 0.268 g/cm²) in the distal radius after 6 months. Computed tomography (120 kV, 150 mA; Aquilion 64 CXL, Toshiba Medical Systems Corporation, Tochigi, Japan) showed that the implanted allograft-BM contained active bone formation at 2 months and new, mature bone at 4 months (Fig. 4).

The re-implantation surgery was performed 4 months after the bone stock reconstruction operation (66-years). The bone loss spaces had been completely filled with newly formed bone (Fig. 5). Newly formed bone from the allograft-BM showed active osteoblast-like lining cells near to the bone tissue (Fig. 6). During the surgery, patella tendon was partially detached from tibia tubercle. Therefore, it was fixed rigidly using suture anchor. Finally, stable fixation of a new prosthesis with stems and metal augmentations was achieved using only cement containing antibiotic (1 g of vancomycin per 40g-batch of bone cement) (Fig. 5). The new prosthesis was stable at the latest follow up (4 months after re-implantation surgery).

3. Discussion

The sinus tract is the contraindication of one-stage exchange arthroplasty for the treatment of infected TKA. Moreover, a two-

stage exchange provides a better outcome with the control of infection.² In general, two-stage exchange is recommended in this case, however, we chose three-stage exchange. Bone stock reconstruction is important to obtain stable prosthesis fixation. Although large amounts of allograft-bone are needed in this case, the strength is weak to obtain stable prosthesis fixation. Furthermore, the nonunion risk of these allograft-bones seemed to be high. Therefore, we decided to reconstruct the bone stock first.

The repair of large bone defect remains a major orthopaedic challenge because very large autograft-bone is not available because of donor-site morbidity. Although allograft-bone is a good candidate, it has osteoconductive, but not osteoinductive, properties. Furthermore, there are risks of nonunion and bone resorption.³ In this case, the huge and extensive bone defects were clearly poor environments for osteoinduction and bone union. Sufficient osteogenesis was not expected after only allograft-bone transplantation. Therefore, we performed a tissue engineering-based technique by combining the allograft-bone with BM. BM contains mesenchymal stem cells (MSCs), and MSCs have the capability to differentiate into osteogenic cell types.⁴ BM and. BM (or MSCs) combined with allograft-bone composites exhibit osteogenic activity and have already been used for bone reconstruction.^{5–10} The bone fusion rate of allograft-BM was higher than that after allograft-bone treatment only.¹¹ However, the number of MSCs in BM is small. To resolve this problem, MSCs has to be purified from BM, and a large number of MSCs can be obtained by cell culture expansion, where MSCs are attached to tissue culture plastic *in vitro*, mitotically expanded, and even differentiated along the osteogenic lineages with osteoinductive agents. However, these techniques must be performed in a cell processing center under good manufacturing practices for clinical use.¹² Because ordinary hospitals rarely have such facilities, we developed a simpler alternative method.

Several reports have shown the effects of TPTD for the local bone defect^{13,14} and the union between the host and allograft-bone.¹⁵ The remarkable potential of TPTD as an adjuvant therapy for allograft-bone repair in animal models was also reported.¹⁶ Furthermore, TPTD treatment increases the differentiation of osteoprogenitors and augments bone formation around structural allograft-bones.¹⁷ TPTD also increases bone volume and reduces tumor engraftment and volume in human breast cancer skeletal

Fig. 3. Bone stock reconstruction by treatment with allograft bones loaded with bone marrow.

(a) Intra-operation digital image of the distal femur. (b) Anteroposterior and (c) lateral view X-rays of the left knee. First, one allograft bone was cut into several block shapes and placed in the medullary cavities of the distal quarter of the femur and proximal quarter of the tibia as bone plugs. Chipped allograft bones mixed with bone marrow were implanted in the bone defects. White arrows (a) show the chipped allograft bones mixed with bone marrow.

Fig. 4. Computed tomography scans of the implanted allograft bones loaded with bone marrow.

(a) 1 month, (b) 2 months, and (c) 4 months after the bone stock reconstruction surgery. Computed tomography showed that the implanted allograft bones loaded with bone marrow contained active bone formation after 2 month and mature bone after 4 months. White lines show the level of the axial views.

Fig. 5. The re-implantation surgery for the total knee prosthesis.

(a) Intra-operation digital image of the distal femur. (b) Anteroposterior and (c) lateral view X-rays of the left knee. Good bone formation from the chipped bone allografts loaded with bone marrow was confirmed during the re-implantation surgery. The huge and extensive bone loss defects were completely filled with newly formed bone. White arrows (a) show the good bone formation from the chipped bone allografts loaded with bone marrow. The re-implantation surgery (b and c) for the total knee prosthesis was performed 4 months after the bone stock reconstruction operation.

Fig. 6. Histology of newly formed bone from the chipped bone allografts loaded with bone marrow.

A piece of newly formed bone from the chipped bone allografts loaded with bone marrow was harvested during the operation. Active osteoblast-like lining cells were observed near the bone tissue. Hematoxylin and eosin staining; original magnification: $\times 40$.

metastasis mice model.¹⁸ Moreover, TPTD induces differentiation of MSCs along the osteoblast lineage by enhancing bone morphogenetic protein signaling.¹⁹ In addition, the increased maturation of circulating osteoblast precursors was observed after TPTD treatment.²⁰

In conclusion, the treatment of allograft-BM achieved successful bone formation in the huge and extensive bone loss. Furthermore, TPTD might enhance this bone stock reconstruction. This useful method that does not require *in vitro* culture or cell processing may be a good option for the bone stock reconstruction surgeries in ordinary hospitals.

Conflicts of interest

None.

References

- Steinblocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. *J Am Med Assoc.* 1949;140:659–662.
- Romano CL, Gala L, Logoluso N, Romano D, Drago L. Two-stage revision of septic knee prosthesis with articulating knee spacers yields better infection eradication rate than one-stage or two-stage revision with static spacers. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:2445–2453.
- Wheeler DL, Enneking WF. Allograft bone decreases in strength *in vivo* over time. *Clin Orthop.* 2005;435:36–42.
- Caplan AL. Mesenchymal stem cells. *J Orthop Res.* 1991;9:641–650.
- Stiehler M, Seib FP, Rauh J, et al. Cancellous bone allograft seeded with human mesenchymal stromal cells: a potential good manufacturing practice-grade tool for the regeneration of bone defects. *Cytotherapy.* 2010;12:658–668.
- Zamiri B, Shahidi S, Eslaminejad MB, et al. Reconstruction of human mandibular continuity defects with allogenic scaffold and autologous marrow mesenchymal stem cells. *J Craniofac Surg.* 2013;24:1292–1297.
- Fernandes MBC, Guimaraes JAM, Casado PL, et al. The effect of bone allografts combined with bone marrow stromal cells on the healing of segmental bone defects in a sheep model. *BMC Vet Res.* 2014;10:36.
- Hatzokos I, Stavros SI, Iosifidou E, Karataglis D, Christodoulou A. Autologous bone marrow grafting combined with demineralized bone matrix improves consolidation of docking site after distraction osteogenesis. *J Bone Joint Surg Am.* 2011;93:671–678.
- Stanovici J, Le Nail LR, Brennan MA, et al. Bone regeneration strategies with bone marrow stromal cells in orthopaedic surgery. *Curr Res Transl Med.* 2016;64:83–90.
- Verboket R, Leiblein M, Seebach C, et al. Autologous cell-based therapy for treatment of large bone defects: from bench to bedside. *Eur J Trauma Emerg Surg.* 2018;10.1007/s00068-018-0906-y [Epub ahead of print].
- Hart R, Komzak M, Okal F, Nahlik D, Jajtner P, Puskeiler M. Allograft alone versus allograft with bone marrow concentrate for the healing of the instrumented posterolateral lumbar fusion. *Spine J.* 2014;14:1318–1324.
- Campana V, Milano G, Pagnano E, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mater Sci Mater Med.* 2014;25:2445–2461.
- Fassio A, Rossini M, Viapiana O, et al. New strategies for the prevention and treatment of systemic and local bone loss; from pathophysiology to clinical application. *Curr Pharm Des.* 2017;23:6241–6250.
- Kitaguchi K, Kashii M, Ebina K, et al. Effects of single or combination therapy of teriparatide and anti-RANKL monoclonal antibody on bone defect regeneration in mice. *Bone.* 2018;106:1–10.
- Reynolds DG, Takahata M, Lerner AL, O'Keefe RJ, Schwarz EM, Awad HA. Teriparatide therapy enhances devitalized femoral allograft osseointegration and biomechanics in a murine model. *Bone.* 2010;48:562–570.
- Takahata M, Schwartz EM, Chen T, O'Keefe RJ, Awad HA. Delayed short course treatment with teriparatide (PTH1–34) improves femoral allograft healing by enhancing intramembranous bone formation at the graft-host junction. *J Bone Miner Res.* 2012;27:26–37.
- Sheyn D, Yakubovich DC, Kallai I, et al. PTH promotes allograft integration in a calvarial bone defect. *Mol Pharm.* 2013;10:462–471.
- Swami S, Johnson J, Bettinson LA, et al. Prevention of breast cancer skeletal metastases with parathyroid hormone. *JCI Insight.* 2017;2:10.1172/jci.insight.90874 [Epub ahead of print].
- Yu B, Zhao X, Yang C, et al. PTH induces differentiation of mesenchymal stem cells by enhancing BMP signaling. *J Bone Miner Res.* 2012;27:2001–2014.
- D'Amelio P, Tamone C, Sassi F, et al. Teriparatide increase the maturation of circulating osteoblast precursors. *Osteoporos Int.* 2012;23:1245–1253.