



Case report

Abundant heterotopic bone formation following use of rhBMP-2 in the treatment of acetabular bone defects during revision hip arthroplasty

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ABSTRACT

Revision hip arthroplasty in the setting of periacetabular bone loss presents a significant challenge, as options for restoring bone loss are limited. Recombinant human bone morphogenetic protein-2 may offer a solution by promoting bone growth to restore bone stock before implant reimplantation. Here we present a case of a patient with a periprosthetic acetabulum fracture, resulting in pelvic discontinuity as the result of significant periacetabular bone loss. Using a staged approach, periacetabular bone stock was nearly entirely reconstituted using recombinant BMPs and allograft, which resulted in stable fixation, but with abundant heterotopic bone formation. Recombinant BMP-2 offers a useful tool for restoring bone stock in complex hip arthroplasty revision cases with periacetabular bone loss; however, caution must be used as overabundant bone growth as heterotopic ossification may result.

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Introduction

Periacetabular bone loss in revision hip arthroplasty presents a significant challenge, with limited options for reconstruction. Here we present a case where recombinant human bone morphogenetic protein (rhBMP)-2 was utilized to promote bone reconstitution, however was associated with abundant heterotopic ossification.

Case history

A 42-year-old woman with rheumatoid arthritis on prednisone presented to the emergency department with severe right hip pain and inability to bear weight after sustaining a twisting injury while stepping off a curb. She previously had a right total hip arthroplasty performed 20 years ago and revised 1 year prior for loosening. She reported never having a pain-free interval after her revision. Physical examination revealed significant pain with any right hip range of motion and inability to perform active straight leg raise.

Radiographs revealed a right transverse periprosthetic acetabulum fracture with an acetabular component that was grossly loose and protruded. Extensive osteolysis and bone loss were noted in both the ischium and ilium (Fig. 1). Laboratory workup at that time yielded erythrocyte sedimentation rate and C-reactive protein levels that were within normal limits. Hip aspiration was also performed, which was negative for infection.

After discussion with the patient, the decision was made to proceed with acetabular component revision for aseptic loosening. Prednisone was held before her surgery. At the time of surgery, she was found to have a grossly loose acetabular component with a complex pelvic discontinuity involving transverse fractures through the anterior and posterior columns as well as a large segmental posterior wall fragment. There was significant osteolysis, which precluded stable fixation of an immediate revision acetabular component. The decision was made to perform the revision in a staged fashion because the extent of bone loss would have limited bony contact (<30%) with the implant as well as insufficient screw fixation. In addition, there was concern for the ability to achieve bony union of the discontinuity, given her history of rheumatoid arthritis. A 2.8-cc dose of rhBMP-2 and 10 mL of demineralized bone matrix were placed overlying the discontinuity site and 150 cc of allograft bone chips within the acetabulum. The femoral component was retained. (Fig. 2) She remained toe-touch weight-bearing postoperatively.

The patient underwent the second stage of her revision 7 months later.

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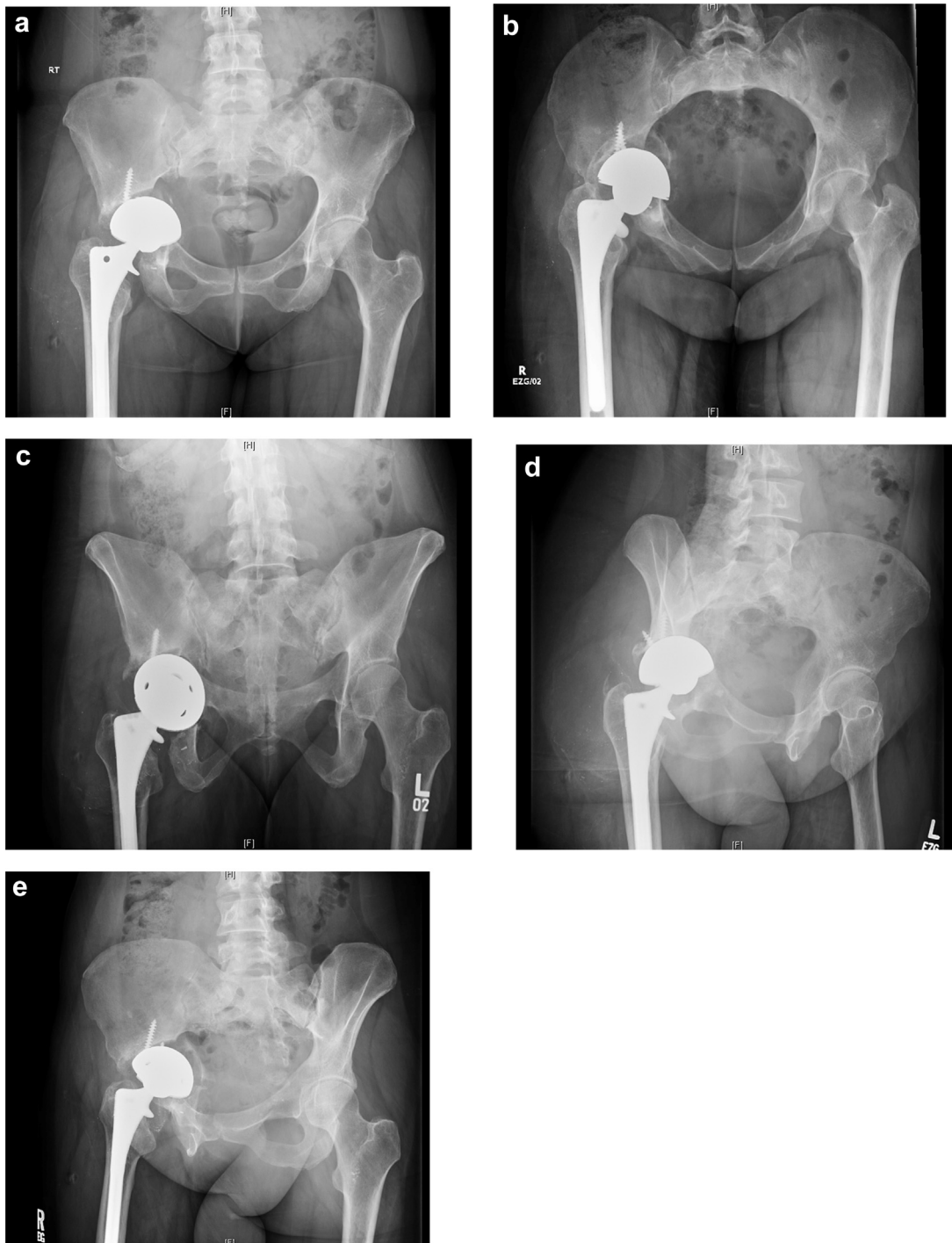


Figure 1. Preoperative pelvic radiographs. Anteroposterior (AP) (a), inlet (b), outlet (c), obturator oblique (d), and iliac oblique (e) images.

Intraoperatively, she was found to have completely healed the pelvic discontinuity with reconstitution of the entire acetabulum with restoration of the anterior and posterior columns as well as dome and medial wall. Furthermore, an abundance of heterotopic ossification (HO) had also formed around the acetabulum, which was excised. (Fig. 3) An acetabular component with trabecular metal augments and 5 screws for fixation were placed and supplemented with autograft from the excised HO. (Fig. 4)

The patient had an uneventful perioperative recovery and was discharged from the hospital. By 4 months postoperatively, her pain had nearly resolved, incisions were healed, and radiographs

demonstrated early osteointegration of the acetabular augment and implant. At 2-year follow-up, she was doing very well without pain and walking without limp.

Discussion

Basic science

Bone morphogenetic proteins (BMPs) were discovered in 1965 when implantation of demineralized bone matrix led to new bone formation, suggesting unknown local factors resulted in

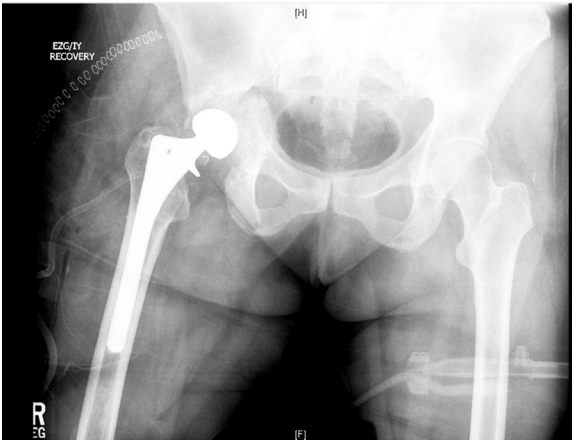


Figure 2. Postoperative radiograph taken immediately after the first staged surgery.

osteogenesis by autoinduction [1]. BMPs are now understood to be members of the *TGF- β* supergene family and play a crucial role in the differentiation of the osteogenic lineage and fracture repair [2]. Osteogenic BMPs, particularly BMP-2 and BMP-7, function through tyrosine-kinase receptors to activate the *Smad* protein-signaling pathway (Fig. 5). This, in-turn, activates gene transcription factors to differentiate mesenchymal cells into osteogenic and

chondrogenic phenotypes [2-5]. Induced bone formation occurs because a chemical gradient leads to chemotaxis of chondrogenic and osteogenic cells, followed by vascular invasion and cell differentiation [6,7]. In addition to its primary function in regulating bone tissues, the BMP cascade also functions to regulate cell growth, movement, and homeostasis [8,9]. During fracture healing, BMP subtype expression occurs in a specific temporal fashion to regulate cartilage calcification and osteoblast recruitment [10].

Two BMP subtypes have been approved by the US Food and Drug administration (FDA) for clinical use in humans: rhBMP-7 (also known as osteogenic protein-1, initially distributed by Stryker Biotech, Hopkinton, MA, but now not available in the United States) and rhBMP-2 (INFUSE, Medtronic, Inc. Fridley, MN) [11]. rhBMP-2 is approved by the US FDA for 3 specific indications: 1. Treatment of lumbar interbody fusion using metallic cage, rhBMP-2, and collagen sponge carrier; 2. Treatment of open tibial shaft fractures treated with intramedullary nail fixation; and 3. As an alternative to autogenous bone graft for sinus augmentation and localized alveolar ridge augmentation for defects associated with extraction sockets.

Multiple animal studies have demonstrated that rhBMP-2 leads to local bone and cartilage formation [7] and has a time- and dosage-dependent effect to accelerate cartilage formation and bone mineralization [7,12]. BMPs improve bony ingrowth into porous metal implants and lead to more rapid initial callus formation, maturation, and greater early torsional strength in animal models [13-17].

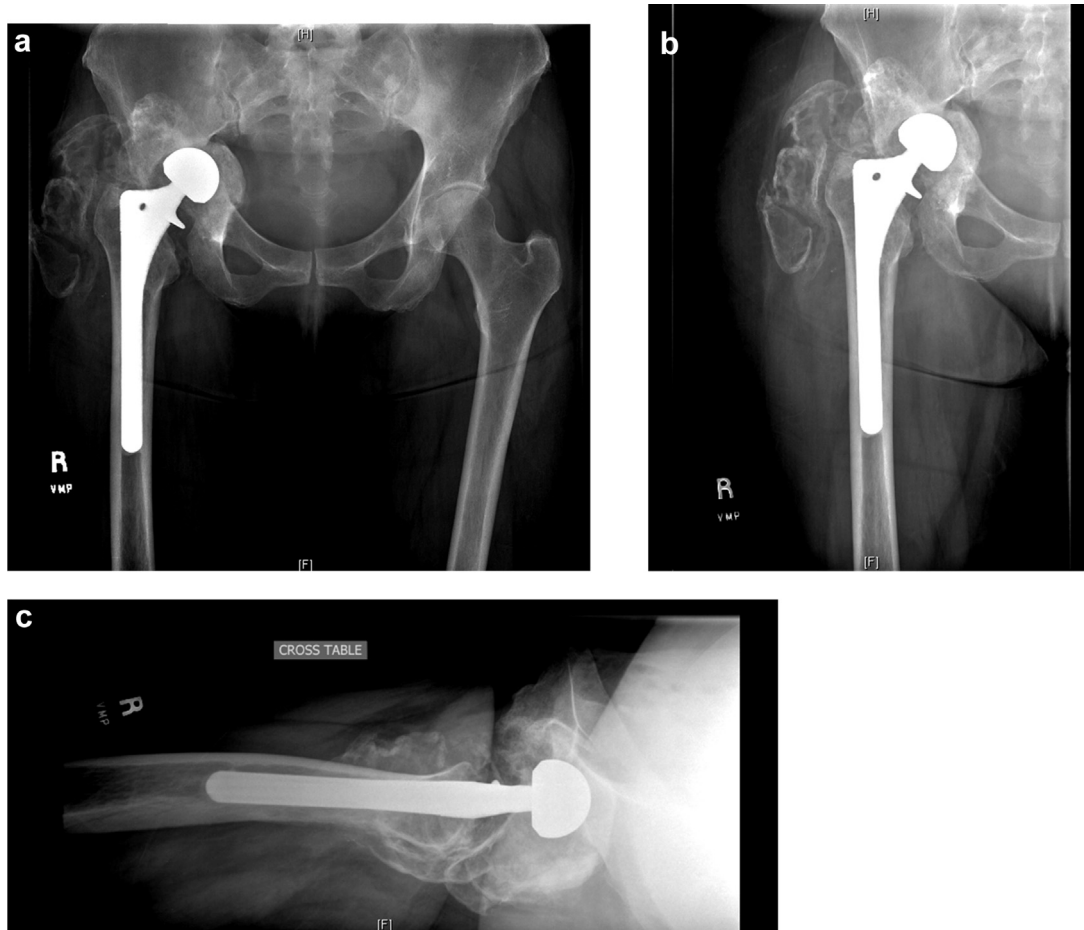


Figure 3. Two months after explant and bone grafting postoperative radiographs of the pelvis (a), hip AP (b), and lateral (c).

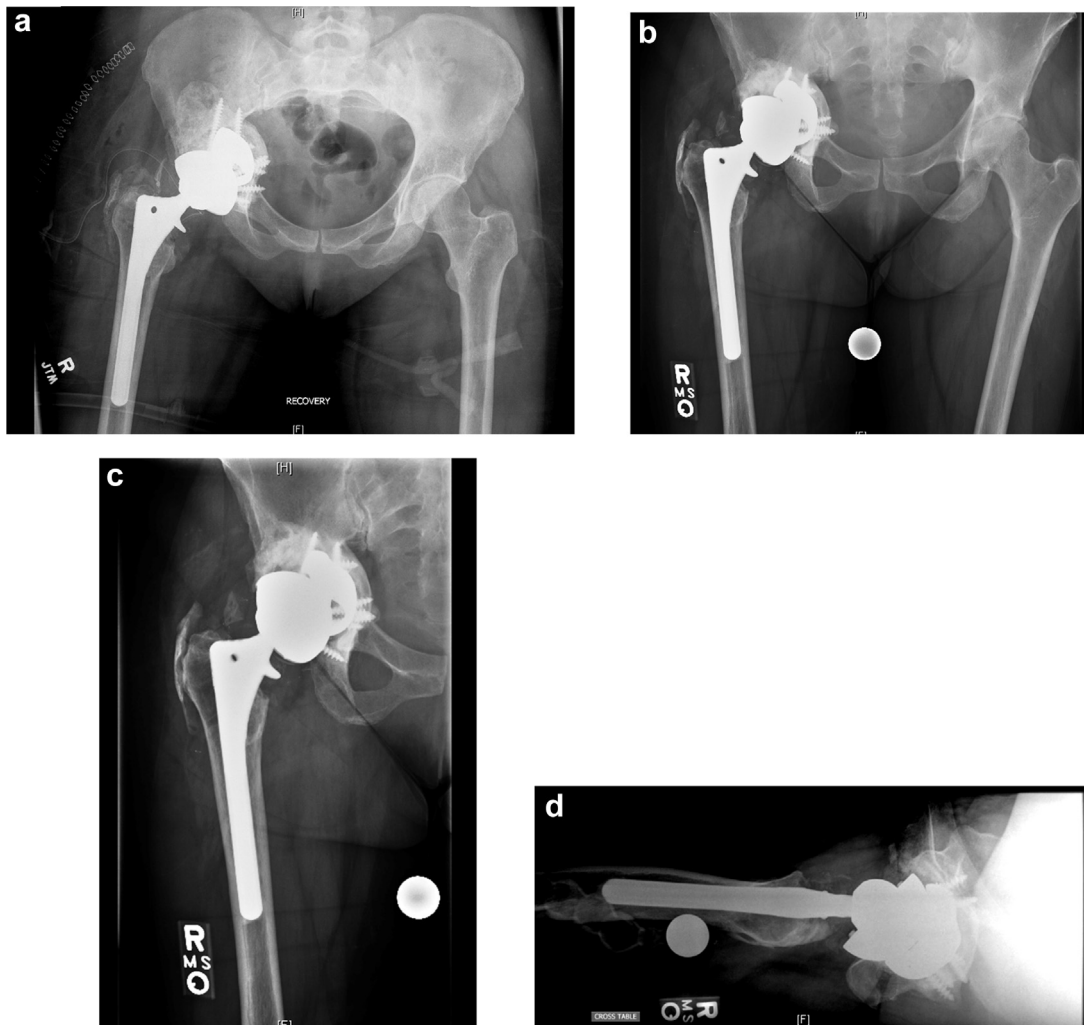


Figure 4. Radiographs taken after the second stage of the procedure. Immediately postoperative (a), 8 months postoperative AP pelvis (b), AP hip (c), and lateral hip (d).

Clinical utilization of BMPs

Advantages of BMPs include the potential to achieve similar union rates as cancellous autograft but with decreased rates of donor site pain [18–20]. In the spine literature, initial reports found that BMPs provide comparable posterolateral fusion rates as local autograft [21–26]. A randomized study by Hurlbert et al [27] found that patients receiving rhBMP-2 demonstrated a higher rate of radiographic fusion than those who received autograft, but found no differences in clinical outcomes. Michielsen et al [28] found analogous fusion rates in patients receiving either rhBMP-2 or autologous iliac crest graft. In the trauma literature, Govender et al [29] randomized 450 patients with open tibia fractures to intramedullary nail fixation with or without rhBMP-2. Though patients who received high-dose rhBMP-2 required fewer secondary interventions and demonstrated accelerated fracture healing, intramedullary reaming was also performed more frequently in the BMP group. In patients treated with reamed intramedullary nails for open tibial shaft fractures, Lyon et al [30] randomized patients with closed tibial shaft fractures to reamed, locked intramedullary nails with or without rhBMP-2. No differences in infection rates, time to radiographic union or pain-free weight-bearing was noted; however, patients receiving rhBMP-2 had increased rates of venous thromboembolism and postoperative HO.

As the clinical usage of BMPs has increased, its safety has been called into question [31,32]. Carragee et al initially reported concerns, pointing out that many initial trials were sponsored by industry and may have under-reported adverse events [19,32–34]. In some studies, BMPs have shown no advantages over autograft and may lead to greater risk of complications such as osteolysis and bony resorption, ectopic bone formation, retrograde ejaculation, wound complications, life-threatening cervical soft-tissue swelling, and nerve root radiculitis [34–37]. Caution should be taken during placement of BMPs because displacement or migration has led to ectopic bone formation, which can potentially affect nearby critical structures [38]. Through December 2011, the FDA received 62 reports of adverse events following rhBMP-2 use in nonspinal applications, including wound complications, HO formation, and local inflammation [39].

Though concerns of BMPs as a pro-oncogenic protein have been raised, a large study using the Medicare database found no increased risk of malignancy [40].

BMPs have been studied in the treatment of acetabular bone defects due to osteolysis, as the alternatives of bone allograft or autograft have not reliably produced bony ingrowth in a porous implant [41,42]. Bragdon et al implanted porous-coated titanium acetabular components after creating central acetabular defects in a canine model. Those receiving rhBMP-2 had near-complete bony

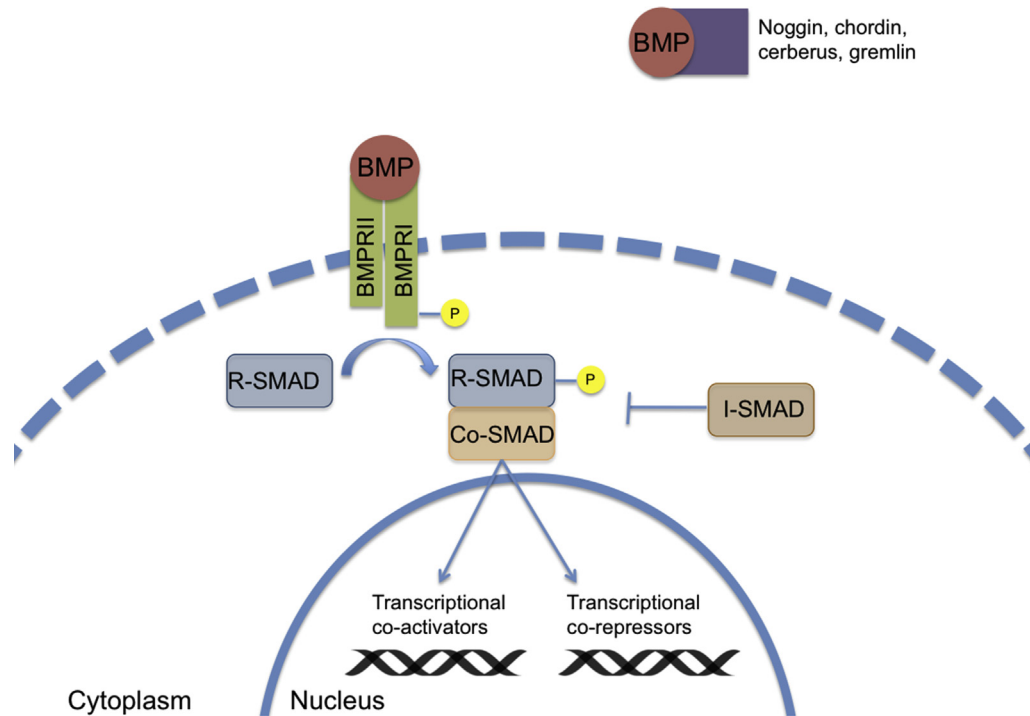


Figure 5. BMP gene transcription pathway.

bridging, whereas defects in the control group remained empty with fibrous tissue [43]. Hoshino et al [44] performed total hip arthroplasty after creating proximal femur and acetabular defects in a canine model. Hips receiving rhBMP-2 demonstrated complete radiographic healing of both femoral and acetabular defects, as compared to none in groups receiving carrier only. Histologic examination of hips receiving rhBMP-2 demonstrated bony ingrowth of woven bone and fibrous tissue compared to minimal ingrowth and persistent bony defect in the control group. Barrack et al [45] created central acetabular defects in a canine model and performed porous-coated titanium total hip arthroplasties. Hips treated with rhBMP-7 had more complete radiographic bony healing, greater histologic new bone formation, and increased ingrowth into the porous metal implant. Hips receiving rhBMP-7 had even greater bony ingrowth into the implant than hips treated without an acetabular defect. Jensen et al found the addition of rhBMP-7 increased bone formation and mechanical stability of a hydroxyapatite-coated implant in a canine model [46,47].

Cook et al reported a clinical case where rhBMP-7 was used with femoral head allograft to successfully reconstruct a large acetabular defect [48,49]. Similarly, Jager et al reported the successful usage of rhBMP-2 in a staged fashion to bridge a large acetabular defect [50]. Kärholm et al [51] published a retrospective case–control series investigating the use of rhBMP-7 for bone loss in acetabular revision. Impaction grafting using morselized femoral head allograft in conjunction with 3.5 mg of rhBMP-7 was performed. Control cases were matched for age, gender, type of defect, type of implant, and volume of allograft used. The authors found no differences in Harris hip score or reported pain between groups, but 2 patients in the BMP group required acetabular revision for loosening and proximal component migration.

Heterotopic ossification

We present a case where the therapeutic use of recombinant BMPs was associated with HO [52,53]. Conditions such as

fibrodysplasia ossificans progressiva, where mRNA expression of BMP-4 is upregulated, and progressive osseous heteroplasia have shed light on the pathways for ectopic bone formation [54,55]. Current animal models of HO are based on the surgical implantation of BMPs, which induce heterotopic bone formation through endochondral ossification. rhBMP has been shown to create ectopic bone when implanted in subcutaneous tissue in a dose-dependent fashion [7,56,57]. Though the exact mechanism of HO remains unknown, 3 key phases for its development have been identified: 1. Inductive signaling pathways, 2. Inducible osteoprogenitor cells, and 3. A microenvironment conducive to osteogenesis [52].

Rates of significant HO formation following total hip arthroplasty ranges from 1% to 27% and is associated with male gender, advanced patient age, increased soft-tissue trauma, and hematoma formation [58–60]. Fracture morphology, early timing of surgery, and associated abdominal and thoracic injuries correlate with the development of heterotopic bone formation following acetabular surgery [61,62]. Both nonsteroidal anti-inflammatory medications and perioperative radiation therapy have been used for HO prophylaxis following major hip surgery; randomized trials have shown both to be effective [60,63–65]. Though some reviews contend radiation as superior [66], a recent meta-analysis of more than 1200 patients found similar efficacy between the 2 treatment modalities in preventing heterotopic bone formation [67]. Patient compliance in completing 6 weeks of nonsteroidal anti-inflammatory medication prophylaxis are thought to contribute to differences seen between the 2 treatment methods [68,69].

Other reports have been published describing heterotopic bone formation following the therapeutic use of rhBMPs. In a randomized trial, Haid et al reported that the use of rhBMP-2 in lumbar interbody cages was associated with new bone formation into the spinal canal or neuroforamina in 71% patients [70,71]. Wysocki and Cohen reported pathologic bone formation in the triceps musculature following rhBMP-7 use when treating a distal humerus fracture nonunion [72]. Axelrad et al reported 4 cases of substantial

heterotopic bone formation in the upper extremity following the use of rhBMPs for fractures [73]. Boraiah et al reported heterotopic bone formation in 59% of patients when rhBMP-2 was used during surgical treatment of acute tibial plateau fractures [74].

Summary

Management of periacetabular bone loss presents a challenge during total hip arthroplasty; we present a case of staged acetabular revision using recombinant BMPs and allograft to effectively restore bone stock, followed by implantation of an acetabular component with trabecular metal augments, leading to stable fixation and satisfactory clinical results at 1 year post-operatively. However, abundant heterotopic bone formation was noted within the soft tissues around the hip after the first stage and thus we urge caution when using recombinant BMPs in this application.

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