Management of Bilateral Subtrochanteric Femur Fractures with Internal Fixation and rhBMP-7 in a Patient with Osteopetrosis

A Case Report and Review of the Literature

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ABSTRACT

Osteopetrosis is a group of conditions characterized by defects in osteoclastic function resulting in defective bone resorption. Clinically, the condition is characterized by dense, sclerotic, deformed bone, which despite increased density radiographically, often results in increased propensity to fracture and delayed union. Bone morphogenetic proteins are molecules that have been shown to have osteoinductive properties, and proved effective in the treatment of nonunions. We describe the first report of a patient with a history of osteopetrosis and bilateral subtrochanteric femur fractures, treated with internal fixation and BMP grafting.

Osteopetrosis, originally described by Heinrich Albers-Schonberg in 1904 [1], is now known to represent a group of conditions characterized by defects in osteoclastic function resulting in defective bone resorption.[2] Clinically, the condition is characterized by dense, sclerotic, deformed bone, which despite increased density radiographically, often results in increased propensity to fracture.[3] Despite the increased bone density, problems with fracture healing are often reported.[4] We describe a patient with a history of osteopetrosis who first presented to our institution with an acute traumatic right subtrochanteric femur fracture and subsequently developed a stress fracture at a similar location in the contralateral extremity. To our knowledge, this case is the first reporting of the use of bone morphogenetic proteins in the treatment of a fracture in a patient with osteopetrosis.

CASE REPORT

The patient is a 27 year old male with a history of osteopetrosis who presented to the Emergency Department after slipping on ice. The patient reported twisting his right lower extremity before stabilizing himself with his left leg. He denied falling or striking his leg against anything. He complained of immediate sharp pain in his right hip area, and was transported to the emergency department via ambulance.

The patient had a known history of osteopetrosis and had previously suffered a left humerus, a left tibia, and a right femur fracture. All prior injuries had been managed non-operatively. The patient was not taking any medications and was not being followed by any physician for continued management of his osteopetrosis diagnosis.

On examination, the patient was afebrile with stable vital signs. His pelvis was stable on exam with no tenderness to palpation. His left hip was non-tender throughout a full range of motion. His right hip was tender to palpation and with any passive motion. The right lower extremity was neurologically intact to light touch sensation along all distributions. Motor function was intact in all lower extremity groups but the patient was unwilling to range his right hip secondary to pain. All extremities were well perfused with palpable distal pulses.

Radiographs revealed sclerotic bone consistent with osteopetrosis. X-rays of his pelvis, right hip, right femur, and chest were obtained. There was a predominantly transverse fracture at the level of the lesser trochanter with a mild degree of posterior displacement of the distal fracture fragment (Figure 1).

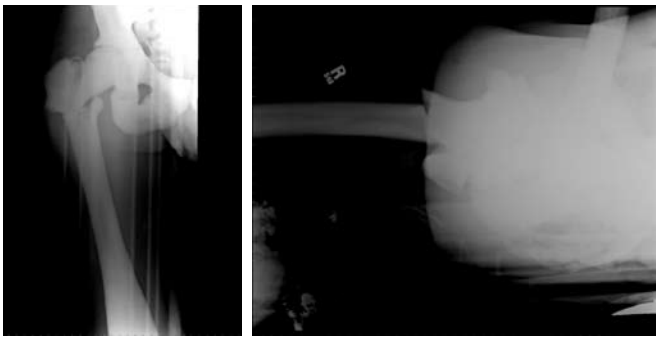

Figure 1A Figure 1B

Figure 1: *A*. AP and *B*. lateral radiographs of the patient's right hip at the time of initial presentation to the Emergency Department.

The patient was taken to the operating room the following morning for open reduction internal fixation with a right angle Dynamic Compression Screw (DCS) implant (Synthes, Inc. Westchester, PA). Due to the extreme density of the patient's bone, the use of numerous drill bits was required with a prolonged drilling time. Constant irrigation and drilling pauses

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were used throughout the drilling process to prevent heat necrosis. An 8-hole DCS plate with a 65mm lag screw was used and was secured to the femur with seven 4.5 mm cortical screws. The wound was closed over a drain and the patient was taken to the recovery room without incident.

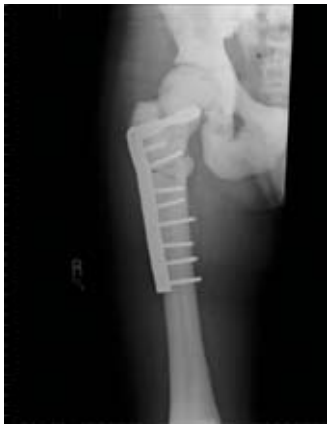

Figure 2: AP radiograph of the patient's right hip four weeks after initial fixation.

The patient did well post-operatively and was discharged to a rehabilitation facility on his third day after surgery. He was initially allowed to be toe-touch weight bearing only on his operative side. The patient was seen in follow up and was allowed to advance to 50% partial weight bearing four weeks after his procedure. At that time, the patient continued to complain of some pain when ambulating, and also had discomfort with internal and external rotation of his hip. Radiographs demonstrated the hardware to be intact with satisfactory alignment of the fracture fragments but with no evidence of callus formation or other signs of progressive healing (Figure 2). The patient returned for follow up eight weeks after his surgery and radiographs still failed to demonstrate any evidence of healing progression. In addition, a stress fracture of the patient's contralateral femur was noted at the same level as the fracture managed operatively on the right side two months earlier. (Figure 3)

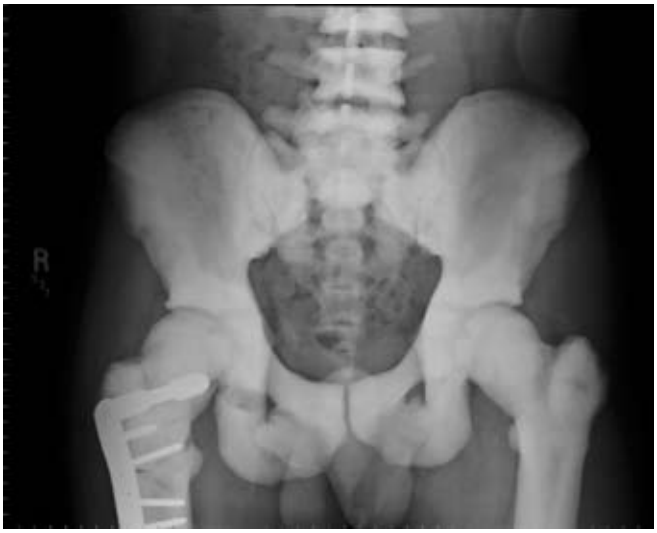

Figure 3: AP radiograph of the pelvis obtained eight weeks after initial fixation. Note the lack of healing progression of the right femoral fracture and the stress fracture now visible in the left femur.

After discussion with the patient, it was recommended that he should return to the operating room to undergo internal fixation of his stress fracture of the left femur along with bone morphogenetic protein (BMP) grafting to both his new left sided fracture site as well as his prior right sided fracture site. Grafting was recommended given the poor progression of healing up to this point, with a concern for early hardware failure. The use of BMP graft was recommended in lieu of iliac crest graft given the expected difficulty of harvesting osteopetrotic crest as well as the questionable use of osteopetrotic bone as a useful grafting material.

The patient was brought to the operating room and underwent internal fixation of his stress fracture with a 6-hole DCS construct utilizing a 60 mm lag screw. Once again, due to the extreme density of the patient's bone, a prolonged drilling time with multiple drill bits was required. Both fracture sites were grafted with a dose of BMP-7 (OP-1®, Stryker Biotech, Hopkinton, MA).

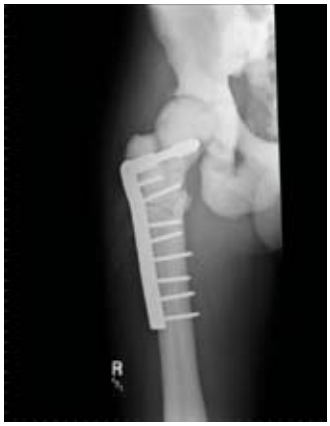

Figure 4: AP radiograph of the right hip obtained six weeks after grafting with BMP-7 demonstrating some initial callus formation.

The patient's post-operative course was unremarkable and he was discharged to a rehabilitation facility. Follow up radiographs obtained at approximately six weeks from his second surgery demonstrated the hardware to be intact with callus formation noted at the initial fracture site on the right side (Figure 4). He had weaned off all narcotics and was able to walk without a walker but felt safer with the support of a cane or a single crutch. He did, however, continue to complain of pain in his right hip with ambulation. At 5 1/2 months post-op, the patient continued to ambulate with a mildly antalgic gait, and a CT scan was obtained. This demonstrated continued evidence of fracture healing, but the fracture lines were still visible. Expectant management of the patient has continued, and 2 years after his operations he continues to have visible, but less sharply defined fracture lines on radiographs of his right

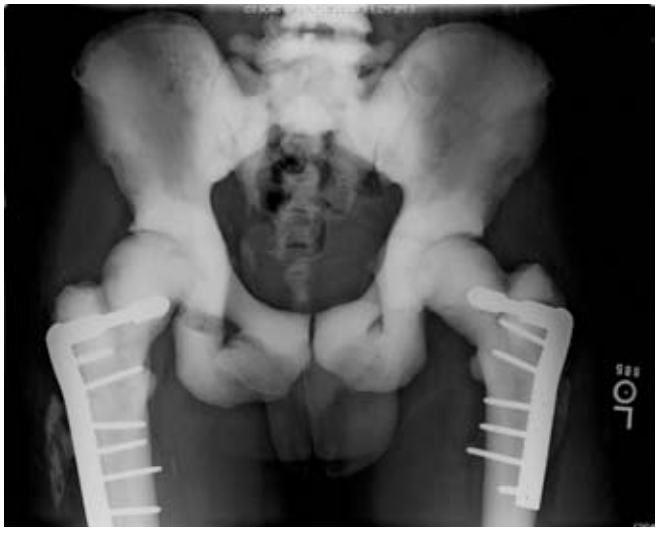

Figure 5: AP radiograph of the pelvis at 2 year follow up demonstrating continued, although improved, appearance of the right sided fracture. The left sided stress fracture is no longer visible.

hip. There are no fracture lines visible at the site of his stress fracture (Figure 5). There has been no evidence of loosening or hardware failure. The patient currently ambulates with a nonantalgic gait and does not require any assistive devices. The patient is now a dentist and states he can work all day on his feet without difficulty, but does admit to some fatigue with mild bilateral discomfort at the end of long days. He does not run or participate in other athletic activities. He has 5/5 motor strength in all lower extremity muscle groups. He has not had any other orthopedic injuries since the time of his stress fracture.

DISCUSSION

Osteopetrosis represents a group of conditions with defects in osteoclastic function resulting in defective bone resorption.[2] Traditionally, osteopetrosis has been categorized on the basis of clinical features. This lead to the description of three main types: autosomal recessive infantile or malignant variety, autosomal recessive intermediate variety, and autosomal dominant osteopetrosis, which was further divided into two primary subtypes.[2,3,4] Patients with autosomal dominant osteopetrosis (ADO), also known as the "adult" or "benign" form of osteopetrosis, typically present later in life, with as many as 50% of patients remaining asymptomatic.[3,4] Type I ADO is distinguished from Type II ADO by the presence of thickening and osteosclerosis of the cranial vault and diffuse vertebral sclerosis, as opposed to basal skull and vertebral end plate thickening that is characteristic in the type II form of the disease.[3,4] In addition, type I patients are not as frequently subject to the increased risk of fracture and delayed healing that marks patients with type II ADO.[4] We believe our patient is afflicted with Type II ADO based on his history and clinical presentation.

Advances in genetic analysis have now allowed classification of the disorder based on the particular gene involved, although a significant percentage of patients have no identifiable gene defect.[2] About 60% of patients with severe autosomal recessive osteopetrosis (i.e. infantile or malignant form) have a defect in the TCIRG1 gene, which codes for a particular osteoclast H+-ATPase proton pump.[5] A defect in chloride channels, caused by mutations in the CLCN7 gene, is responsible for another 15% of patients with the severe autosomal recessive form of the disorder. Interestingly, the CLCN7 gene also appears to be responsible for many cases of the intermediate autosomal recessive form as well as most, if not all cases of the autosomal dominant type II variety of osteopetrosis.[2] The variability seen in the clinical presentation of the disorder may be the result of modifier genes or the specific mutation that is present.[6] The first defect described in human osteopetrosis was a lack of carbonic anhydrase II activity, now ascribed to mutations in the CAII gene. However, this defect appears to be responsible for less than 5% of cases of severe autosomal recessive osteopetrosis.[7]

The clinical manifestations of osteopetrosis span a wide spectrum. The most severe forms result in death within a few months of birth, usually due to obliteration of the marrow cavity resulting in pancytopenia and infectious complications, while the most benign forms allow patients to have a normal life expectancy but with a high incidence of fractures, usually with a transverse fracture pattern.[2,3,4] Increased bone density of the entire skeleton is the radiographic hallmark of osteopetrosis. In severe cases there is complete absence of the medullary canal, and this lack of differentiation between the cortex and the medullary canal often results in a bone-in-bone appearance.[4,8] Failure of remodeling gives rise to characteristic metaphyseal splaying resulting in a club-like deformity of tubular bones and an "Ehrlenmeyer flask" appearance of the femurs, as is apparent in the patient presented (Figure 6).[4,8] A similar process in the spine results in a sandwich-like appearance or "rugger jersey" spine.[4]

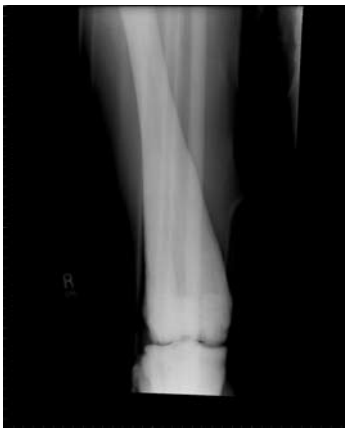

Figure 6: AP radiograph of the patient's distal femur demonstrating the "Ehrlenmeyer flask" appearance characteristic in osteopetrosis.

Armstrong, et al. surveyed the membership of the Pediatric Orthopedic Society of North America in an attempt to elucidate the optimal methods of treatment for fractures occurring in patients with osteopetrosis. A consistent response from the participants regarded the difficultly in placing an internal fixation device secondary to the increased bone density. Often, non-operative treatment was reported to produce satisfactory results, although the rate of healing was frequently noted to be prolonged. Similar problems were seen with internal fixation with case reports of delayed union of up to 2 years.[4] This is possibly related to the fact that the fracture callus in patients with osteopetrosis has been shown to be abnormal with continuation of unorganized woven bone and a lack of lamellar organization at 1 year even in healed fractures.[9]

Urist first described osteoinduction, later ascribed to bone morphogenetic proteins (BMPs), in 1965.[10] There are now at least 18 different BMP molecules described, of which at least 8 have been shown to have osteoinductive properties.[11] Currently, only two BMPs have been commercialized through recombinant gene technology, BMP-2 (Infuse®, Medtronic Sofamor, Minneapolis, MN) and BMP-7 (OP-1®, Stryker Biotech, Westchester, PA), and these are limited to approved applications in trauma and spinal fusion.[12] In particular, OP-1® is approved for use in recalcitrant nonunions of long bones. Multiple studies have demonstrated that the use of BMPs is comparable to autografting in the treatment of nonunions without the morbidity associated with autograft harvesting and with a lower risk of infection than those patients treated with autograft.[11,12] To our knowledge this is the first report of the use of BMP in the management of a fracture in a patient with osteopetrosis.

Laboratory studies have demonstrated several properties of BMPs of clinical significance. The osteoinductivity of BMPs follows a dose-response ratio in which the local concentration of a BMP determines the clinical response. If the concentration is too low, inadequate bone formation will occur; if the dose is too high, heterotopic ossification might be expected, although this has not been shown to occur under physiologic conditions.[11,13] BMPs have also been shown to not only affect osteoblast activity, but also to stimulate osteoclast activity and osteoclastogenesis.[14] In fact, higher doses appear to often result in initial localized bone resoprtion.[11]

The patient with osteopetrosis is at risk for frequent fractures with subsequent delayed union or nonunion. This paper reports the results of a patient with bilateral femur fractures and osteopetrosis treated with internal fixation and BMP-7 grafting after his first fracture failed to show any signs of healing 2 1/2 months after operation. It is noteworthy that radiographs 1 month after application of BMP-7 to the previously non-healing side demonstrated promising callus formation. However, at 2 years follow-up, the patient still had visible fracture lines on his x-rays. Immediately after the application of BMP, enough osteoclast activity was apparently stimulated to allow for the initiation of fracture healing. As shown in large animal models, the efficiency of BMPs is hampered due to rapid local clearance of the proteins. The use of buffered delivery systems resulted in less than 5% of the initial dose remaining at the application site, and delivery systems using gelatin foams, collagen, or calcium phosphate pastes only resulted in about half of the original dose being maintained.[11] Therefore, it is possible that although the grafting initially stimulated some bone resorption and formation, the local concentration of BMP declined too rapidly to result in efficient healing of the fracture. As more effective carrier devices and sophisticated application techniques are developed, the use of BMPs may be a viable option to assist in the treatment of fractures in patients with osteopetrosis.

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