A Case Study: The Role of Allograft Bone in the Late Reconstruction of Osteosarcoma of the Fibula

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Abstract

Background: Osteosarcoma of the fibula is a devastating condition that may lead to lower extremity amputation. Limb salvage is possible with the use of en bloc fibular resection, flap reconstruction of soft tissue deficit, and adjuvant radiation. History of radiation at the site of intended arthrodesis, florid instability of the joint complex, and history tobacco use and diabetes mellitus would complicate the potential for solid fusion. Allogenic bone graft augmentation can significantly improve the healing potential. In terms of efficacy, it has been found to be equivalent to autograft.

Methods: We present an interesting case where secondary management of the limb was undertaken nearly three decades after index fibulectomy for osteosarcoma in a patient with multiple high-risk comorbidities. The ankle had an advanced abnormal tibiotalar tilt, with residual post-traumatic changes to both ankle and subtalar joint. A tibiotalocalcaneal arthrodesis was performed with intramedullary rod and augmented with allogenic cellular bone matrix.

Result: Radiological fusion was obtained at 10 weeks of both the subtalar and ankle joint. Patient obtained a rectus-plantigrade limb, and is currently ambulating pain-free.

Conclusion: Bone healing in the lower extremity is notoriously unpredictable and beholden to several variables. The use of an allogenic cellular non-structural bone graft with standardized concentrations of MSCs and angiogenic growth factors was our choice in this case. This allograft is an effective and safe alternative to autograft for use in high-risk foot and ankle fusions in nicotine-dependent, and diabetic patients.

Keywords: Osteosarcoma; Fibula; Radiation; Allograft

Introduction

Osteosarcoma of the fibula is a condition requiring multidiscipline input during the primary management stage. The most favorable result could be achieved with amputation, but limb salvage is often possible with the use of en bloc fibular resection, flap reconstruction of soft tissue deficit, and adjuvant radiation. Depending on the patient’s skeletal development at the time of index procedures, this strategy can result in excellent clearance of tumor but with the long-term sequel of disabling gait mechanics. The effects of distal fibular resection can include ankle valgus deformity [20,32]), abnormal talar tilt [33,38], knee instability with traction of the common peroneal nerve [34,36] and growth plate disturbances of the distal tibia.

The rarity of distal fibular resection and variety of antecedent pathology has resulted in many different long-term management strategies and overall lack of consensus about the best way to address the ankle in its aftermath [31,33,35,37]. It is conceivable to repair residual lateral ankle ligaments or perform peroneal tenodesis to the distal tibia [30], reconstruct the lateral ankle with the use of auto or allograft, or perform tibiotalar arthrodesis with or without fusion of the subtalar joint [31].

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In the presented case, secondary management of the limb was undertaken nearly three decades after index fibulectomy for osteosarcoma. The ankle was unstable with resultant chronic inversion subluxation sprains and osteoarthritis. The quality of articular cartilage, plastic and developmental deformation of the tibial plafond, and subtalar joint damage by proxy all contributed to limitation of options with fusion the only reasonable course of action.

History of radiation at the site of intended arthrodesis and florid instability of the joint complex alone would complicate the potential for solid fusion, but additionally, the presented case would almost certainly be a reluctant fusion given the patient's comorbid tobacco use and insulin-dependent diabetes.

Smart application and selection of bone graft augmentation can significantly improve healing. Autologous corticocancellous graft carries all of the necessary bone forming elements and structure, however it has known limitations. Donor-site morbidity is a very real concern [2-4,27-29]. Iliac crest autograft can result in persistent numbness, hematoma, deep infection, chronic pain, and iatrogenic fracture, with an overall occurrence between 2.4 and 9.5% [2,3]. Autograft from the more distal lower extremity is inferior in both quantity and quality and carries an increased risk of donor-site morbidity. Baumhauer, et al. found that proximal tibia, distal tibia, and calcaneal autograft locations were associated with a 12% risk of clinically-significant pain at 24 weeks and 8.5% risk of the same at 52 weeks post-operatively [4]. O’Malley, et al. confirmed the presence of residual symptoms in patients undergoing calcaneal autograft harvest with 13.8% of subjects reporting various forms of morbidity at an average of 2.8 years’ follow up [5]. Autologous bone graft harvest also prolongs and complicates the procedure, frequently requiring additional anesthesia in the form of deeper sedation, airway protection, or spinal anesthesia, where the primary operation might only call for a regional block with moderate sedation.

The argument for controlled cellular content has arisen from empirical evidence that graft health influences bone healing [8]. McAlister, et al. confirmed that a minimum concentration of biologic potential of pluripotent cells is necessary to measurably enhance fusion [7]. There is also a correlation between new bone formation leading to improved rate of union and number of fibroblast colony-forming units. These important variables are strongly influenced by the systemic health of the patient, suggesting that the source of autograft may be compromised in the very subgroup that requires the most assistance in bone healing.

Autograft was once regarded as the gold standard for fusion or fracture healing augmentation in foot and ankle surgery. Orthobiologic processing methods have improved such that specialized allograft can achieve the same results without resultant donor-site morbidity or reliance on an ideal host. The consistency and reliability of graft quality, which has previously been at issue, has come under greater scrutiny and standardization has improved. A recent review article found by logistic regression of data from 159 publications that efficacy of auto- and allograft were equivalent in foot and ankle fusions [11].

The academic and research goals in presenting this case are modest, but in the burgeoning field of orthobiologics for foot and ankle reconstruction it is a necessary prelude and counterpart to higher-level research in this area. Through anecdotal case review, we aim to demonstrate that rearfoot and ankle fusion are possible and can be achieved safely without iatrogenic effects in a patient with severely sub-optimal bone-healing potential through the application of an allogenic cellular bone matrix that includes all components of periosteal, cortical, and cancellous bone in addition to controlled immunogenic potential and concentration of live cells.

Graft Characteristics

BIO4 (Osiris) is an allogenic cellular bone matrix with formulation including all components of periosteum, cancellous, and cortical bone. Processing is carried out using aseptic technique. All tissues are soaked in anti-microbial solution until bioburden is sufficiently minimized. The final product has preserved bone periosteum with Vascular Endothelial Growth Factor (VEGF), which supports angiogenesis. Cell types in BIO4 are identified using fluorescence activated cell sorting (FACS) analysis. Quality control mandates a minimum of 70% cell viability, 600,000 viable cells per cc with expression of known mesenchymal stem cell (MSC) markers CD105 and CD166, and

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presence of angiogenic growth factors, which are important for bone repair at sites of damage; these include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). The presence of VEGF was confirmed using ELISA, which showed higher amounts of endogenous angiogenic growth factors compared to similar viable bone allograft formulation lacking periosteum. An In vitro assay demonstrated the angiogenic potential by exposing cells sensitive to angiogenic signals to BIO4 and visualizing via fluorescence microscopy the formation of tubes, marking the initial step in creation of new blood vessels.

Case Study

A 42-year-old male presented for multifactorial problematic ankle condition. The patient had a near complete fibular resection secondary to osteogenic sarcoma at age 15. He underwent seven operations related to the same, which included rotational muscle flap and skin grafting that were necessary as part of the en bloc resection. As a result of the fibular resection and radiation, he was subsequently cancer-free, however the ankle remained chronically unstable, subject to repeated sprains, and ultimately developed arthritis of the tibiotalar and subtalar joints. His medical condition was complicated by tobacco use and insulin-dependent diabetes mellitus.

X-ray findings were consistent with near complete fibular resection with remaining fibular head only, advanced tibiotalar tilt, post-traumatic arthritic change at the ankle as well as the subtalar joint (Images 1a-b).

Clinically, the patient had approximately 35 to 40 degrees of talar tilt. Lateral soft tissue scarring was present, extending from the mid-tarsal joint to the lateral leg. There was a semi-reducible rearfoot varus deformity. His angle and base of gait was consistent with a rearfoot varus and unstable lateral ankle. His range of motion was considerably diminished in dorsiflexion at the tibiotalar joint and near complete loss of eversion at the subtalar joint. Plantar flexion and inversion were excessive at both the ankle and subtalar joints respectively. The patient had very limited to minimal eversion power at the ankle. He ambulated with a limp and with an apropulsive pattern consistent with his right-sided deformity.

The patient presented to discuss total ankle replacement. There were obvious concerns regarding the lack of fibula and lateral ankle instability that would ultimately doom an ankle replacement to early failure. Therefore, a tibiotalar and subtalar joint arthrodesis with fixation and bone grafting was proposed as the most optimal and durable surgical procedure for the patient’s deformity.

The surgical procedure was performed with the patient in the supine position, with a popliteal block and spinal anesthetic. Anterolateral approach was taken consistent with the prior osteosarcoma resection incision.

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Both the tibiotalar joint and the subtalar joint were exposed accordingly, entering the deep soft tissue and capsular structures. The tibiotalar joint was prepared first with a powered osteotome rongeur, curette, standard osteotome and mallet, and sagittal saw. The cartilage of the superior talus and undersurface of the tibia were resected in reciprocal fashion and by near identical means.

Once both joints were resected of all cartilaginous surface, the foot was positioned in the neutral to slightly everted position at the subtalar joint in a neutral to slightly externally rotated position at tibiotalar joint.

The steinman pin for the intramedullary rod was then placed through the plantar central lateral calcaneus through extending into the distal one third central medullary tibia.

Once the position of Steinmann pin was confirmed for final placement of the intramedullary rod, the drilling and reaming was then performed in sequence through the plantar incision over the Steinmann pin through the calcaneus, talus, and tibia. After drilling and reaming were complete, the tibiotalar and subtalar joints were then grafted with 10 cc of BIO4 through the posterior medial portion of the subtalar joint as well as the posterior portion and medial gutter of the tibiotalar joint.

An appropriately-sized intramedullary nail was chosen, measuring 11 mm in diameter x 150 mm in length. The nail was placed via the alignment guide through the plantar incision into the calcaneus, talus, and tibia. Calcaneal screws were then placed posterior to anterior, locking nail in the rearfoot. Compression was then performed via the mechanism associated with intramedullary nail and alignment guide, across both the subtalar and the tibiotalar joints accordingly. The final position was confirmed via multiple views of intraoperative fluoroscopy, the locking screws were then placed in the tibia via medial to lateral approach in typical fashion.

The alignment jig for the intramedullary nail was removed. At this time, the final bone grafting was then performed by placing 2.5 cc of the BIO4 into the most lateral portion of the subtalar joint near the sinus tarsi. An additional 2.5 cc of the BIO4 bone graft was placed in the most anterior portion of the tibiotalar joint.

Incision inspection was performed seven days post-operatively. The wound remained coapted and infection free with radiographic follow-up at two weeks post-surgery. X-ray was consistent with well-positioned tibiotalar and subtalar joints, intramedullary rod fixation, joint and bone graft visualization (Image 2a-b). At 6 weeks, x-ray was consistent with signs of both tibiotalar and subtalar joint visualization with minimal bone graft visualization. No bone graft reabsorption, minor joint line visualization. 9 - 10 week x-ray was consistent with complete consolidation of the subtalar joint and tibiotalar joint, no bone graft visualization, and unchanged intramedullary rod fixation with locking screws of the calcaneus and tibia (Image 3a-b).
Discussion

Our case is an example of a perfect storm of risk factors for non-union. The combined effect of a chronically-unstable tibiotalocalcaneal joint complex, adjuvant local radiation, tobacco abuse, and diabetes are confounding to an arthrodesis effort. A solid intramedullary nail construct was imperative to the success of this procedure, but prior literature and mounting anecdotal evidence bears proof that enhanced biology at the site of fusion is a necessary inclusion for any degree of reliable outcome. The use of an allogenic cellular non-structural bone graft with standardized concentrations of MSCs and angiogenic growth factors was our choice in this case for delivering the needed raw materials for stimulation of new bone across the two intended arthrodesis sites. While autograft could have been used as a supplement, our decision to exclude an additional procedure was based on the history of harvest complications, increased operative time, and likelihood of sub-optimal autograft biology in a patient with co-morbid medical conditions.

Bone healing in the lower extremity is notoriously unpredictable and beholden to several variables. While our case included multiple possible risk factors, there are countless other ways a patient can suffer extreme limitation of fracture or fusion site healing. Poor health, dynamic arthrology, extensive soft tissue injury, and lack of anatomic or pathologic blood supply are difficult features to correct; they can plague the success of bone healing. Under adverse conditions with multiple or severe immutable risk factors for non-union, successful fracture healing or arthrodesis can be as low as 60% even with excellent surgical, medical, and rehabilitative care [1]. Failed procedures commonly result in ongoing pain and often require revision surgery. In addition to risks of infection, chronic pain, and limb loss, the potential monetary burden to patients and health system cannot be understated. Most surgeons faced with this peril are in agreement that some form of graft augmentation is mandatory in any case involving known risk for bone healing.

An ideal bone graft combines osteogenic, osteoconductive, and osteoinductive qualities to facilitate the normal physiologic phases of primary bone healing. Synthetic bone substitutes or decellularized bone are available in nearly limitless quantities, but they have limited osteoconductivity, poor cell retention, and suffer from immune rejection. Cadaveric bone has been scrutinized high rates of pathogen transmission. The rate of bacterial and fungal isolates from cadaveric allograft bone can reach 25%. There are also legitimate concerns regarding time from death, effects of freezing, and donor variation. There was a time when autograft in isolation or combined with a bone substitute, allograft, or xenograft was the only way to incorporate all three necessary traits of bone healing without risking bi-incompatibility.

There are now several allografts available that feature viable endogenous bone-forming cells; the graft material we used in this case series resembles its predecessors with some minor variations. Mesenchymal Stem Cells (MSCs) are the workhorse of the graft with Platelet-derived growth factors (PDGF) and fibroblast growth factors functioning in a supportive role as recruiters of MSCs during fracture healing [16,17]. MSCs, numbering at least 600,000 with 70% guaranteed to be viable in this product, are embryonically active in creating

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mesoderm and eventually all connective tissue. Derived from periosteum and surrounding soft tissue [22], they can replicate multiple times without losing the ability to differentiate, and have the potential to become osteoblasts and produce a variety of bone morphogenetic proteins (BMPs), making them a reservoir of cells for new bone growth [10]. In fracture repair, as well as in arthrodesis, MSCs initiate the formation of a cartilaginous callus that is then replaced by new bone, which bridges the fracture or arthrodesis site [24]. Kallai., et al. found that implantation of MSCs engineered to express the BMP-2 gene healed fracture nonunions [15].

The main theoretical drawbacks of stem cell transplantation include vascular embolization and immune rejection. Embolization is less of a concern in distal extremity work and immune rejection has been addressed by removing problematic antigens from the synthetic graft during processing. Minamide., et al. showed that high doses of MSCs (1x10^8) were necessary for fusion to occur with the same success as with high concentrations of BMP or with autograft. Lower doses (1x10^6) were not as effective. When MSC-enriched preparations are co-administered with low concentrations (< 5 ug mL^-1) of BMP2, the rate of fusion can be comparable with autograft. In this way, a bioengineered tissue with controlled numbers of MSCs can function as well or better than autograft for arthrodesis without the harvest-associated complications or risk of unrestrained tissue proliferation [12-14].

Material handling properties are an important design consideration. Graft material without structural scaffold to encourage bone healing or sufficient pliability or viscosity to enable reliable placement and retention can be a deterrent to maximal effect. BIO4 features a porous osteoconductive cancellous scaffold and periosteum for inclusion of angiogenic growth factors and improved physical cohesiveness of the material.

**Conclusion**

BIO4 is an effective and safe alternative to autograft for use in high-risk foot and ankle fusions in nicotine-dependent patients and diabetics. Methodological shortcomings could threaten the validity of our conclusions. The radiographic analysis for fusion was determined by close evaluation of plain films without additional information from advanced imaging. In a study comparing clinical fusion with radiographic fusion degree as determined by computed tomography (CT), only minimal (25 - 49%) osseous bridging was necessary to achieve symptom-free clinical fusion [26]. Interpretation of clinical time to fusion as a function of bone graft efficacy is only partially reflective. We also did not incorporate the use of a validated clinical scoring system. Despite these limitations, we believe that the results of this investigation could be used in future meta-analysis or motivate prospective cohort studies or randomized controlled trials with the confidence that cellular allogeneic bone grafts in foot and ankle orthopaedic surgery are safe and effective.

**Bibliography**


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