



Mesenchymal Stem Cell Allograft in a Nonunion Fibular Fracture: A Case Report

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Abstract

Ankle fractures are common injuries treated by the foot and ankle surgeon. The majority of stable, uncomplicated, minimally or non-displaced distal fibular fractures will heal with adequate immobilization and conservative treatment. However, some patients will develop a symptomatic partial union or nonunion. Several factors can contribute to a nonunion following a fracture including smoking, obesity, infection, and diabetes mellitus. In cases of surgical reconstruction, augmentation with osteobiologics consisting of mesenchymal stem cells can be utilized to enhance osseous healing of the nonunion site. We present a successful case of a distal fibular nonunion repair with the use of a partially demineralized allograft bone combined with adipose derived mesenchymal stem cells to promote bone healing. At six months follow-up, there was solid bone healing of the fibular nonunion with complete resolution of symptoms.

Introduction

Ankle fractures are an increasingly common injury to the ankle joint. The incidence of ankle fractures is approximately 187 fractures per 100,000 people per year [1]. Ankle fractures in general occur from a rotation force on the ankle with the most typical mechanism related to a fall from a height or stairs [2]. Other etiologies include sport activity, blunt trauma, and motor vehicle accident. The most common fracture is the lateral malleolus followed by bimalleolar, trimalleolar and isolated medial malleolar fractures [2-4]. The two common classification systems used for ankle fractures are the Lauge-Hansen and Danis-Weber classifications. The Lauge-Hansen system is based on the position of the foot and the direction of the force at the time of injury [5]. The supination-external rotation mechanism is the most common type of ankle fracture [6,7]. The Danis-Weber classification is based on the level of the fibular fracture to the ankle joint [8]. In the average patient, the standard treatment for displaced ankle fractures is open reduction with internal fixation [9].

A nonunion following a fracture can present a difficult challenge for the foot and ankle surgeon. The incidence of a fibula nonunion is 0.3% to 5.4% [10]. A successful union can be influenced by several risk factors that are associated with poor bone healing including smoking, osteoporosis, diabetes mellitus, obesity, steroid use, advanced age, nutritional deficits, alcohol, vitamin D deficiency, thyroid disorders, and nonsteroidal anti-inflammatory drugs [11,12]. These factors can also affect ankle fracture healing [13-17]. There have been numerous prognostic factors associated with a fibular nonunion following fracture including fracture displacement, oblique fracture pattern, degree of bone loss and fracture combination, and high-energy injuries. A nonunion is typically classified as either a hypertrophic or atrophic nonunion according to the vascularity and amount of bone callus formation present on plain radiographs [10]. A nonunion of the distal fibula is considered relatively rare due to the adequate blood supply and minimal biomechanical stress during ambulation. The treatment of the distal fibular nonunion is generally based on the symptoms, fracture characteristics, and type of nonunion [10].

Bone grafts have been utilized for a variety of foot and ankle procedures. Bone grafts can provide structural support, fill a void or bone deficit, and enhance bone healing. The biological principles of bone graft healing include osteoconduction, osteoinduction and osteogenesis. Since autogenous bone grafts possess all three properties, they have historically been the gold standard for the use in nonunion repair for many years. However, harvesting of an autogenous bone graft can result in complications such as donor site morbidity, pain, fracture, seroma and infection [18]. Surgeons have been employing allogenic bone grafts with mesenchymal stem cells (MSCs) in an effort to acquire a more predictable alternative for grafting material. MSCs are precursor cells that have the capacity

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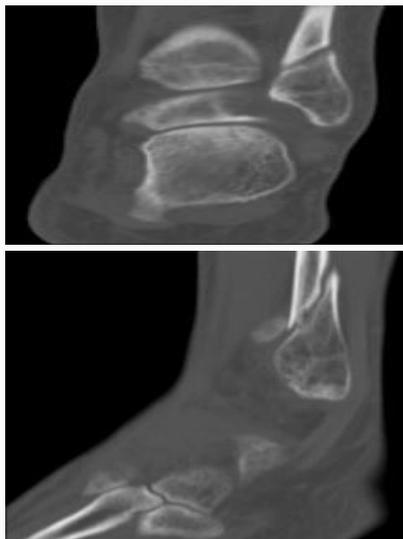


Figure 1: Preoperative CT scans demonstrating the nonunion of the distal fibula.



Figure 2: Preoperative AP and lateral radiographs identifying the distal fibular nonunion.

to differentiate and proliferate into multiple cell lines. Several studies have demonstrated that augmentation with MSCs implemented as a cellular bone matrix is a beneficial adjunct for bone healing [19-23].

We describe a case of a patient that developed a distal fibular nonunion following conservative treatment. Osseous union required operative treatment consisting of resection of the nonunion, internal fixation for stabilization, and use of AlloStem[®] (AlloSource[®], Centennial, CO, USA) to facilitate bone healing. AlloStem[®] bone graft is a combination of partially demineralized cancellous bone and MSCs, which are harvested from donor cadaveric abdomen adipose tissue.

Case Presentation

We present a case of a 46-year-old male who sustained a left



Figure 3: Final 12 weeks postoperative radiographs depicting complete osseous healing of the fibular nonunion.

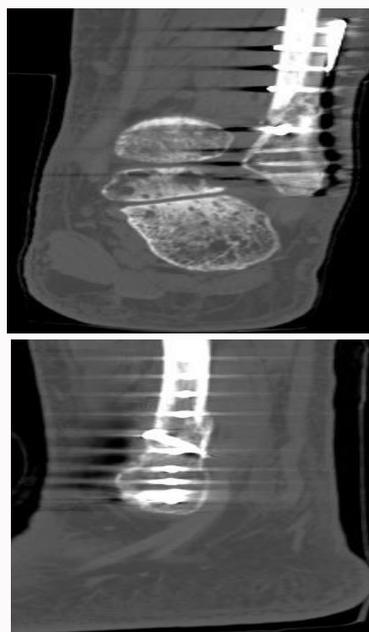


Figure 4: CT scans confirming osseous healing at the fibular nonunion repair site.

distal fibular fracture in January 2014. He recalls walking on uneven ground, felt his ankle “twist”, and collapsed to the ground. The patient described an inversion-type ankle injury and immediately experienced pain and swelling to the left lateral ankle area. He initially treated the area with rest and elevation. However due to the lack improvement in the symptoms, the patient went to an emergency department a few days later where radiographs demonstrated a SER-type II ankle fracture. A cam boot walker and crutches were dispensed along with instructions to be non-weight bearing to the injured ankle. He was referred to another physician who treated the injury conservatively for approximately 3 months. The patient worked as a mechanic and

admitted to weight bearing in the cam boot walker soon after the initial injury. A magnetic resonance imaging study was obtained in June 2014, showing limited osseous formation without solid fusion of the oblique fibular fracture. In addition, a Computed Tomography (CT) scan performed in July 2014 revealed incomplete osseous bridging and evidence of osteopenia (Figure 1).

After six months of persistent pain of the left lateral ankle, the patient presented to the author's clinic in August 2014 for a second opinion. The patient was concerned that his left ankle fracture never healed properly. He had a medical history of hypertension, thyroid disease, heart murmur, and obesity. His medications included tramadol, trazodone, baclofen and losartan. Past surgical history included hernia repair. The patient had no known drug allergies. In addition, he is a current smoker with a 30-pack year smoking history. The patient denied any alcohol or illicit drug use.

On physical exam, his lower extremity neurovascular status was within normal limits. There was moderate pain upon palpation of the left lateral ankle area with minimal edema present. There was no evidence of ankle instability and the ankle syndesmosis appeared to be intact. Plain film radiographs revealed minimal osseous healing of the distal fibula fracture (Figure 2). Due to the persistent pain of the fibular nonunion, we recommended surgical treatment consisting of repair and stabilization of the nonunion with internal fixation, ankle arthroscopy, and application of bone graft. We also recommended smoking cessation, however he continued to smoke throughout the peri operative course. In addition, preoperative labs were obtained including 25-hydroxyvitamin D, ionized calcium, and parathyroid hormone levels. An external bone stimulator was also recommended, however the insurance carrier did not approve the device. The calcium and parathyroid hormone levels were within normal limits. However, the 25-hydroxyvitamin D was relatively low at 32 ng/mL. The patient was subsequently treated with vitamin D 2,000 IU daily and was advised to continue this supplementation until evidence of union.

The patient underwent repair of the distal fibular nonunion with general anesthesia and popliteal nerve block. Ankle arthroscopy was initially employed to evaluate the joint and remove any synovitis present. The articular cartilage appeared normal without osteochondral lesions visualized. Attention was then directed to the nonunion fibular fracture, where a standard longitudinal incision was made overlying the distal fibula. The nonunion was easily identified. The distal fragment was unstable with fibrous tissue noted throughout the nonunion site. There was no osseous healing present. The nonunion was excised and all necrotic tissue was completely debrided to the level of bleeding bone. The defect was also fenestrated with a 2.0 mm drill to promote bleeding across the site. At that time, the AlloStem[®] bone graft was positioned across the previous fracture site. Utilizing lag technique, a 3.5 mm cortical bone screw was placed across the fracture site with excellent compression noted. Next, a lateral plate (Peri-Loc VLP[®], Smith & Nephew, Memphis, TN) was applied with 3.5 mm locking screws as neutralization construct for additional stability. The construct was stressed under fluoroscopy and was noted to be stable. The incisions were irrigated and closed in layers in standard technique. The patient was placed in a posterior splint.

Post-operatively, the patient was instructed to remain non-weight bearing on the operative lower extremity. He was to remain non-weight bearing until radiographic signs of union were present.

At two weeks, he was placed in a below the knee fiberglass cast. Subsequently at three weeks, the patient decided to bi-valve his cast in order to bathe. In addition, he refused application of a new cast at this time. The patient periodically reapplied the bi-valve cast with Velcro straps. The vitamin D level was repeated at three weeks demonstrating a decrease to 31 ng/mL suggesting a non-compliance with the prescribed supplementation. Plain film radiographs were obtained at approximately four weeks, which revealed some evidence of trabeculation across the fibular nonunion. During the post-operative period, the patient remained non-compliant. The patient had missed several appointments and continued to smoke. Since the external bone stimulator was denied by his insurance, the patient opted to create a home made stimulator from a TENS unit. At twelve weeks following the procedure, radiographs revealed evidence of complete osseous union of the previous fibular nonunion (Figure 3). The patient was transitioned to protected weight bearing in a pneumatic cam walker boot. A repeat CT scan was ordered at four months to ensure healing of the operative site (Figure 4). The CT scan revealed 90% osseous union without evidence of hardware complications. The patient was therefore progressed into normal shoe gear. The patient experienced complete resolution of symptoms and was able to ambulate without limitation.

Discussion

The treatment of acute ankle fractures is well reported in the literature. There are numerous documented etiologies of nonunion following fractures including smoking, osteoporosis, diabetes mellitus, obesity, steroid use, advanced age, nutritional deficits, alcohol, vitamin D deficiency, thyroid disorders, and nonsteroidal anti-inflammatory drugs [11,12]. The detrimental effects of smoking on bone and wound healing have been well documented in the literature. Although cigarette smoke has several compounds, the carbon monoxide, nicotine, and hydrogen cyanide are the chemicals that have been implicated in the impairment of bone healing [24,25]. In 2009, Krannitz and colleagues [25] evaluated 46 patients following an elective bunionectomy procedure. The patients in the study were divided into 3 groups including smokers, nonsmokers, and secondhand smokers. The mean time to osseous healing was 69 days in nonsmokers, 120 days in smokers, and 78 days in secondhand smokers. This equates to 42% increase bone healing time in smokers. Cobb "et al." [26] reported a 3.75 to 16 times greater risk of nonunion with an ankle arthrodesis in smokers as compared to nonsmokers. Vitamin D is critical for ideal bone growth and health. Vitamin D deficiency has been associated to poor bone healing, osteoporosis and osteomalacia [27]. In 2010, Bogunovic and colleagues [28] studied 723 patients that had planned orthopedic surgery. They noted that 43% of the patients had insufficient serum vitamin D levels. In addition, Smith "et al." [29] studied 75 patients with foot and ankle fractures. They reported that the vitamin D levels in 47% of patients were below 30 ng/mL and 13% of patients were below 20ng/mL. The authors concluded that vitamin D monitoring and supplementation should be considered in patients with fractures. The patient in our case study had a documented history of smoking and relatively low vitamin D, which we believe contributed to the nonunion.

The use of osteobiologics has become increasingly popular in foot and ankle surgery specifically in the high-risk patient or reconstructive surgical procedures. Although the autograft has become the reference standard, there are limitations and potential complications that may restrict its use in foot and ankle surgery [18,30]. There are numerous

biologic alternatives that exist including allogenic bone, bone morphogenic protein, bone marrow aspirate, demineralized bone matrix, and Mesenchymal Stem Cell (MSC) allograft. MSC allografts have recently been studied in the literature with promising results. In 2014, Anderson and colleagues [19] studied 85 patients with ankle fusions that received either MSC bone allograft or proximal tibia autograft. In the MSC allograft group, 84.1% achieved radiographic fusions in a mean interval of 13.0 weeks. In another study, Scott "et al." [22] evaluated 20 patients with high-risk foot and ankle reconstructions that were augmented with a MSC allograft. They reported a 100% fusion rate with a mean average interval to fusion in 11.6 weeks. Thirty-five percent of these patients admitted to tobacco use. Rush "et al." [21] reported a 91.3% union rate in 23 patients in revision foot and ankle surgery utilizing a MSC allograft. The study noted an overall median time to union of 72.5 days. Interestingly, they also reported a median time to fusion for patients without diabetes mellitus of 66.5 days and a median time to fusion for patients with diabetes mellitus of 91 days. Several studies have shown that adipose derived and bone marrow derived MSCs are effective in bone formation and healing [31-34]. Cellular allografts containing MSCs can be an effective adjunct to enhance osseous healing in foot and ankle arthrodesis and reconstructive procedures. In addition, the MSC allograft is a feasible option in the high-risk patient population.

Conclusion

A nonunion following an ankle fracture can be a devastating deformity. Several factors have been associated to inadequate bone healing and nonunion. The MSC allograft can be a useful adjunct to facilitate bone healing in a nonunion. Allografts containing MSCs can promote osseous healing through the three key principles of osteoconduction, osteoinduction, and osteogenesis. Despite several compounding factors for potential nonunion and the challenges during the post-operative period in this particular patient, the MSC allograft was an excellent choice to promote bone healing. Allografts with MSCs are a reasonable option for foot and ankle surgery.

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