First in Man: Sternal Reconstruction with Autologous Stem Cells

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Sternal nonunion is associated with high morbidity and treated using rigid plate and screw fixation. This is the first reported example of successful sternal reconstruction using adipose-derived stromal vascular fraction (SVF) stem cells in addition to traditional techniques. Mesenchymal stem cells, one component of the SVF, play an important role in bone healing and were therefore used to promote remedial processes in a patient with sternal nonunion. A 3D printed model of the patient's sternum was used for preoperative planning of the plating. Intraoperatively, SVF was isolated using ultrasonic cavitation and previously planned sternal plating was completed. A total of 300 million cells were delivered *via* both local injection and intravenously before chest closure. The patient's pain dramatically decreased, commensurate with healed areas of nonunion by 3 months and maintained at 6 months postoperatively, supported by three-dimensional computed tomography imaging. Utilizing autologous stem cells from the SVF in conjunction with existing plating techniques may provide an optimal platform to stabilize the sternum and promote bone healing, although additional study is recommended. *ASAIO Journal* 2015; 61:e31–e32.

Key Words: sternal reconstruction, autologous stem cells, human adipose-derived stem cells, hADSCs, adipose-derived stromal vascular stem cells, ASC

Sternal nonunion, although rare, is associated with high morbidity.[1] Various fixation techniques have been described with the ultimate goal of rigid fixation and bony union to promote bone healing.[1] Natural bone healing involves many processes, including stem cell involvement. Research has highlighted the important role of mesenchymal stem cells (MSCs) in bone repair, which has lead to the exploration of additional therapeutic options.[2] Emerging treatments include the use of adipose-derived stromal vascular fraction (SVF) cells, which contain multi-potent CD31+, CD34+, CD44+, CD90+, CD73+, and CD105+ cells characteristic of MSCs, in addition to exhibiting mesodermal capacity.[3] Stromal vascular fraction cells have been studied extensively *in vitro* over the past decade. Their potential as progenitor/stem cells has been shown to be equivalent to the properties of pluripotent stem cells or even advantageous to using other populations of stem cells due to their low immunogenicity.[2] These cells can be readily isolated *via* noninvasive lipoaspiration from subcutaneous fat at a much higher yield than other sources, and has since emerged as an alternative tissue source for use in regenerative medicine. These adipose-tissue SVF cells, or adipose-derived stem cells (ASCs), have been used in studies that include cartilage and bone regeneration, wound healing, articular cartilage defects, and tissue regeneration. Because SVF cells can be used without expansion and cell-culture treatment, the stem cells undergo minimal manipulation before clinical use. Though *in vitro* expansion also shows that human MSCs do not seem to undergo malignant transformation, SVF cells are even more safe and efficacious due to the minimal manipulation.[2] Other studies show further evidence that there are various components of crude SVF that act synergistically with ASCs, which may be more clinically beneficial than ASCs alone.[2] Adipose-derived stem cells are also more immunosuppressive than bone marrow-derived stem cells, another common source used in preclinical and clinical studies.[2] There are many current, ongoing clinical trials involving the use of autologous adipose tissue SVF cells for various disease etiologies including osteoarthritis, spinal cord injury, multiple sclerosis, and acute myocardial infarction.[2,4] Although there is always a possibility of side effects from the delivery of stem cells, minimal side effects are expected from SVF MSCs compared with other cell types, because MSCs have been shown to modulate T-cell-mediated immunological responses.[5] Methods of delivery include both intravenous injection and local injection, both of which have been shown to cause cell homing to the site of ischemia or injury.[5–7]

Here, we outline the first reported case of successful sternal reconstruction with autologous stem cells from the SVF. Utilizing this accessible heterogeneous mixture of cells in conjunction with existing plating techniques may provide an optimal platform to stabilize the sternum and promote bone healing.

Case Report

A 65 year old male presented with disabling pleuritic chest pain due to chronic sternal nonunion with bone loss after coronary artery bypass grafting. This began following an episode of severe coughing secondary to upper respiratory tract infection. Three-dimensional computed tomography of the chest (3D CT) showed a comminuted lower sternal fracture and nondisplaced healing fractures of the left fifth and right fifth and sixth ribs. Although the wired upper portion of the sternum remained intact, the lower sternum had fractured in three places and distracted into four principal pieces greater than 5 cm apart (**Figure 1A**). After medical therapy proved unsuccessful, a sternal reconstruction and unilateral pectoralis flap reconstruction was recommended. Given the extensive sternal nonunion, we constructed a preoperative 3D printed image of the patient's sternum augmented with

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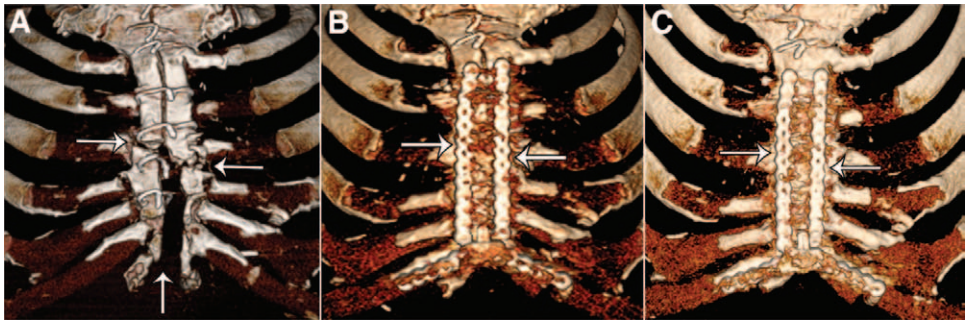

Figure 1. Three-dimensional computed tomography image. Fracture sites and regions of sternal nonunion are indicated by arrows preoperatively (**A**), and healed fractures are indicated by arrows at 3 months (**B**) and 9 months postoperatively (**C**).

biomaterials and mock-prepared the joints and the plating system (Synthes, DePuy, West Chester, PA). This was completed to both plan and practice the procedure in three dimensions before surgery. Although *in vitro* stem cell injection was not completed during the planning phase, after completion of the plating, we identified potential locations for local stem cell injection.

Intraoperatively, we performed sternal plating with bone putty as planned preoperatively, and harvested autologous adipose-derived SVF stem cells with ultrasonic cavitation (IntelliCell Biosciences, New York, NY). A sterile section of the operating room (OR) was used for the SVF isolation procedure, which included a centrifuge, flow cytometer, sonicator probe, and the necessary accessories. Before the plating procedure, lipoaspirate was obtained *via* standard liposuction from the patient's abdomen. The SVF isolation procedure was immediately implemented using the lipoaspirate and completed 1 hour later, by the time the surgeon had completed the sternal reconstruction. This allowed for prompt injection of the freshly isolated, autologous SVF cells: 100 million *via* localized injection and 200 million *via* intravenous injection. The SVF was a heterogeneous population of cells and extracellular matrix that can be used clinically without expansion,[2] and was mostly composed of CD34+ cells with approximately 88% cell viability. Finally, a unilateral pectoralis flap reconstruction was completed before closure.

Serial 3D CT imaging demonstrated fracture healing and closure of areas of nonunion 3 and 6 months postoperatively compared with preoperative imaging (**Figure 1B, C**). Since surgery, the patient has established regular follow up at our outpatient facility. His sternum is stabilized and he now reports minimal to no pain, with normal exercise tolerance. This case is the first reported example in man of successful sternal reconstruction with adipose-derived SVF.

Discussion

Medial sternontomies are the gold standard for many cardiothoracic surgical procedures. Sternal nonunion occurs in approximately 0.5–3% of all patients with standard wire fixation, with greater risk in patients who are on prolonged ventilation, female, older age, or overweight.[8] Treatment options have included repeat circumferential peristernal rewiring, steel banding, polymer tapes, and absorbable sutures, but currently rigid plate and screw fixation is most widely utilized.[1]

Despite improvements in fixation technologies and allogeneic bone matrices, there is no guarantee that healing will occur. As mentioned earlier, human ASC transplantation has shown promise in current orthopedic-related clinical studies, including osteoarthritis and spinal cord injury.[2,4] In addition, the usefulness of ASCs in various wound and bone healing applications has been studied in multiple animal models with evidence that they promote the type of accelerated regeneration we have seen in our patient.[2] Due to the ability to easily acquire both autologous stem cells (adipose-derived and stromal vascular progenitor cells) and native micromatrix from liposuction-derived adipose tissue in the operating room, our method of SVF isolation and application make this an attractive therapeutic option. The engraftment of the SVF and generation of stable bone highlights the importance of cell–matrix combination therapy options, rather than stem cell therapy alone. This has implications for cardiac and orthopedic regeneration.

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