Reconstruction of a Large Posttraumatic Mandibular Defect Using Bone Tissue Engineering With Fresh-Frozen Humeral Allograft Seeded With Autologous Bone Marrow Aspirate and Vascularized With a Radial Forearm Flap

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Introduction: Currently, vascularized autologous bone transplantation is considered the gold standard for large mandibular continuity defect reconstruction. Donor site morbidity is a major concern. Therefore, bone tissue engineering (BTE) seems to be the ideal solution. Fresh-frozen bone allograft is the closest material to autologous bone. The purpose of this clinical report is to show a new technique of large mandibular continuity defect reconstruction using a fresh-frozen humeral allograft seeded with autologous iliac bone marrow aspirate and vascularized with a radial forearm flap.

Methods: A 33-year-old man presented with severe cranio-facial trauma resulting in several fractures of the facial skeleton including a comminuted mandibular fracture from left parasymphysis to left angle, which caused a large continuity defect.

Results: Result at 6 months was aesthetically and functionally satisfactory with osseointegration of the bone graft.

Discussion: The authors chose to use iliac bone marrow aspirate to seed the allograft scaffold since hematopoietic stem cells and mesenchymal stem cell are able to differentiate into osteoblasts, ease of harvest of the iliac crest and its low rate of morbidity. Contemporary biomaterials used for BTE are bioceramic but bone is still the better scaffold to engineer bone and only allografting avoids donor site morbidity. Vascularization is one of the main challenges of BTE; insertion of autologous vascular bundles from pedicle or free flaps is 1 solution. The authors chose the radial forearm flap since the pedicle is long and the authors did not need a great amount of soft tissue.

Key Words: Allograft, bone tissue engineering, mandibular reconstruction

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Large mandibular continuity defects, following severe trauma, tumor-ablative surgery, osteomyelitis, or osteoradionecrosis, severely affect patient's quality of life. They are associated with disfigurement, malnutrition due to masticatory and deglutition impairments, and phonation difficulties if they are left unrepaired.[1] Their reconstruction is challenging for surgeons due to the necessity of functional restoration. The mandible is the only movable load-bearing bone of the facial skeleton, increasing biomechanic difficulties to obtain durable reconstruction. Finally, there are high infection rates given the proximity of the oral flora.[2]

Currently, vascularized autologous bone transplantation, for example, fibula free flap, is considered the gold standard for large mandibular continuity defect reconstruction.[2] The major concern regarding autologous bone harvesting is the morbidity of donor sites.[3,4] Therefore, bone tissue engineering (BTE) seems to be the ideal solution: bony defect repair without donor site morbidity. Several biomaterials are currently investigated[5,6] but the ideal scaffold for BTE combining osteoconductive, osteoinductive, and osteogenic properties has yet to be created.[7] The use of allografts in bony reconstruction is well documented[8] and frequently used in preprosthetic surgery.[9,10] Fresh-frozen bone allograft is the closest material to autologous bone; it exhibits osteoconductive and osteoinductive properties,[11] therefore it is close to an ideal scaffold for BTE.

The purpose of this clinical report is to present a new technique of large mandibular continuity defect reconstruction using a fresh-frozen humeral allograft seeded with autologous iliac bone marrow aspirate and vascularized with a radial forearm flap.

METHODS

A 33-year-old man, suffering from schizophrenia, presented with severe cranio-facial trauma, left shoulder dislocation, and pelvic fracture following a self-defenestration from the 5th floor. He exhibited several fractures of the facial skeleton with a severely comminuted mandibular fracture from left parasymphysis to left angle, right mandibular body fracture, right condylar neck fracture, and many others (Fig. 1A). Initial treatment consisted of reduction of alveolar fractures with arch bars, open reduction, and internal fixation of the different fractures.

While the other fractures healed completely, the comminuted mandibular fracture did not heal and caused a large continuity

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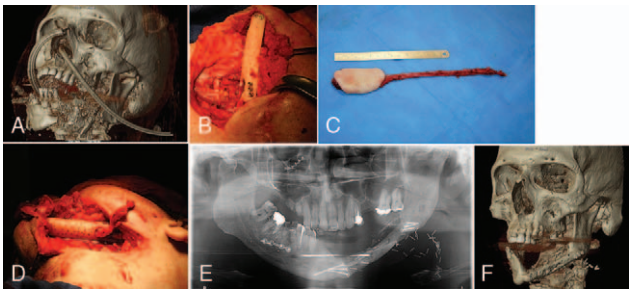

FIGURE 1. (A) Initial posttraumatic CT-scan 3D view. (B) Allograft in the mandibular defect. (C) Radial forearm flap. (D) Pedicle position of the flap through the allograft. (E) Postoperative orthopantomogram. (F) Postoperative CT-scan 3D view. CT, computed tomography; 3D, three-dimensional

defect from left parasymphysis to left angle. It was decided to perform a particular reconstruction to minimize the surgical burden. We planned a procedure using a fresh-frozen humeral allograft as scaffold seeded with progenitor cells collected through iliac bone marrow aspirate and vascularized with a radial forearm free flap. The surgical approach was strictly extra-oral. The frozen humeral allograft (Belgian tissue bank) consisted of half a diaphysis cut longitudinally. It was perforated and shaped to fit the mandibular defect with bone marrow side up, forming a cup-like design. The humeral graft was then fixed with titanium screws to the mandible on each side (Fig. 1B). A left radial forearm flap was raised with a small skin paddle (Fig. 1C). The vascular pedicle was placed to run in the "cup" (Fig. 1D) designed graft with cervical anastomosis of the vascular pedicle (radial vein to facial vein and radial artery to facial artery). The skin paddle was used to monitor the flap. Iliac bone marrow aspirate was performed and was placed in the "cup" designed graft around the vascular pedicle. The technique can be considered as a real BTE demonstrating the possibility to rebuild large bony defects without vascularized bone.

Result at 6 months was functionally satisfactory with osseointegration of the bone graft, resumption of a normal diet and no mouth opening limitation (Fig. 1E and F). A secondary lipofilling procedure was needed 1 year after the first reconstructive surgery to improve the final result. Six months later, the patient was asymptomatic and was satisfied with his aesthetic appearance. One year later, a PET scanner was performed confirming the vitality of the bone graft (Fig. 2). Dental implant placement in the graft has been envisioned but is currently contraindicated due to the poor oral hygiene of the patient.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Helsinki declaration. We obtained an approval with waiver of informed consent by the institutional review board according to French law about retrospective studies.

DISCUSSION

Reconstruction of large bony defect has always been challenging. The first revolution of mandibular reconstruction consisted of osteocutaneous free flaps, especially fibula free flap which was first described in 1989.[12] It is the current gold standard[2] although reconstruction of segmental defect with patient specific implant without vascularized bone transfer has already been described.[13] Bone tissue engineering is expected as the next revolution solving the donor site morbidity and facilitating the shaping of the graft. Three components are necessary to engineer new tissue: cells, signaling molecules, and scaffolds.[14] The associated issue is the vascularization of this newly engineered tissue. Vascularization remains one of the main challenges in BTE.[15]

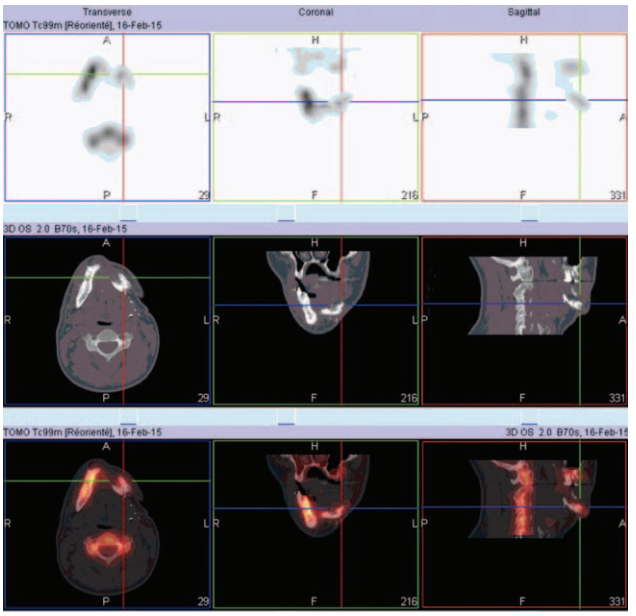

FIGURE 2. Postoperative PET scanner confirming the graft vitality.

Cells are needed in tissue engineering to seed the scaffold. Adult stem cells harvested in the bone marrow are the most used source for bone tissue production.[16] Embryonic stem cells are totipotent and could therefore generate any tissue but their use poses major ethical issues. Cells isolated from different sources than the host generate unfavorable immune responses.[17] Hematopoietic stem cells and mesenchymal stem cells are found in bone marrow, they are able to differentiate into osteoblasts.[18] We chose to use iliac bone marrow aspirate to seed the allograft scaffold according to these evidences, the ease of harvest of the iliac crest, and the low rate of morbidity of the procedure.[19]

Signaling molecules are paramount in an in vitro setting.[18,20] The bone marrow aspirate being placed in the allogeneic bone, it could be inferred that the signaling molecules contained in this bone are sufficient for cellular differentiation in osteoblasts. Furthermore, the classical signaling molecule used in bone differentiation are bone morphogenetic proteins[21] and their sale is currently suspended in France since 2015. Only one molecule was sold but the efficacy was judged to be insufficient (efficacy only evaluated for spinal fusion) by the competent authority to benefit from national reimbursement, the company consequently suspended the sale of the product.

Scaffold in BTE is a 3-dimensional matrix providing a framework where cells can adhere, proliferate, and produce bone tissue.[18] The ideal scaffold is characterized as follows: good bioactivity, good biodegradability, good biocompatibility, predictable rate of degradation, suitable porous structure to promote cell proliferation, vascular ingrowth and nutrient transportation, suitable surface morphology, and physicochemical properties to encourage intracellular signaling, customized shape to adapt the defect.[22] Contemporary biomaterials used for BTE are bioceramic (β-tricalcium phosphate, hydroxyapatite, biphasic calcium phosphate), naturally derived polymers (collagen, chitosan, etc.), and synthetic polymers (polylactic acid, polycaprolactone, etc.). Ceramic have the closest structural and composition similarities with the inorganic part of bone tissue, good osteoconductivity but they are brittle, which can be a concern in load-bearing situations.[23] Naturally derived polymers have good biocompatibility but their mechanical properties are far from those of bone tissue.[24–26] Synthetic polymers offer more versatility in terms of structure (micro or macroscale features such as architecture and

binding groups, porosity, stiffness, and elasticity) but their biocompatibility is not as good as the one of naturally derived polymers.[27,28] To overcome these limitations, synergistic combinations of biomaterials are tested but to date the efficacy of autografts and allografts has not been surpassed.[14] Bone is still the better scaffold to engineer bone and only allografting avoids donor site morbidity. Humeral bone is strong enough to bear the load of mastication.

Small bone grafts such as those used in preprosthetic surgery are vascularized from the surrounding tissue but not large bone graft such as in this case. Vascularization is one of the main challenges of BTE.[15] Remodeling capabilities of severely damaged vascular beds is limited and integrating a fully functional vasculature inside the bone graft is difficult leading to incomplete and inhomogeneous graft viability.[29] The current solution to create vascular tissue alongside bone tissue is distraction osteogenesis. It is a reliable technique but is associated with many downfalls: long treatment duration with a burdensome apparatus, perfect compliance of the patient is mandatory.[30] The other solution for bone tissue vascularization is the insertion of autologous vascular bundles from pedicle or free flaps. Length of the vascular bundle is the main criterion since it must cover the distance from the cervical vessel anastomosis to the parasymphysis while covering the entire graft. We chose the radial forearm flap since the pedicle is long and we did not need a great amount of soft tissue since there were only minimal oral mucosal defect and no skin defect. Anterolateral thigh perforator flap could also have been used but, as discussed, only a minimal amount of soft tissue was necessary. Both flaps are associated with low donor site morbidity[31,32] especially since techniques have been described to close primarily radial forearm flap in cases of small paddle.[33] Fibula free flap morbidity is also low,[34] but we chose to avoid it as the pelvic fracture already led to gait disturbance and pain. This case demonstrated the possibility to rebuild large bony defects without vascularized bone; in this respect, it is genuine BTE. It is in our knowledge the first time that such technique is reported.

CONCLUSION

Bone tissue engineering is the future of maxillofacial reconstruction but many solutions are yet to be found mainly in terms of scaffold components and design and of vascularization. The solution described in this article combines classical techniques and tissue engineering techniques to create a custom made graft relatively easy to perform and to accept by the patient while reducing morbidity.

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