The Brigham and Women's Hospital Face Transplant Program: A Look Back

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Summary: With five face transplants now successfully completed in the United States, the authors look back at their experience with the first face transplant performed in their program. They discuss the process of establishing a face transplant program, the clinical case, and the lessons learned. (*Plast. Reconstr. Surg.* 129: 81e, 2012.)

Composite tissue allotransplantation at the Brigham and Women's Hospital brings full circle a rich tradition of surgical pioneering work. In 1954, the first successful kidney transplantation was performed at the hospital by Dr. Joseph Murray. From this revolutionary feat came the evolution of organ transplantation and now composite tissue transplantation.

Although traumatic defects of facial parts can be treated by reattachment using microsurgical techniques,[1] this option is not always available, and autologous tissues or prostheses are utilized to replace the missing tissues.[2–5] Reconstruction of defects involving the central areas of the face is particularly challenging. Composite tissue allotransplantation provides a major reconstructive advantage over conventional techniques by replacing the missing structures with anatomically identical tissues.

The deleterious effects of immune suppression, including increased incidence of cancer, infections, and end organ toxicity, have been the major limiting factor for allograft transplantation of nonvital organs, including the face and limb structures. Weighing the benefits of non–vital organ transplantation over the risks associated with immune suppression is highly controversial.[6]

Therefore, our group initially developed a protocol in May of 2007 for facial unit transplantation in prior organ transplant recipients already receiving immunosuppressive therapy who needed facial reconstruction.[7] The inability to identify an appropriate recipient, however, led to the expanded protocol "Transplantation of allograft face or facial subunit for treatment of burn-, trauma-, or cancer-related facial defects," which was approved by our institutional review board in March of 2008.

Four goals define the current mission of our program. The first is to provide a superior option for facial reconstruction of complex facial defects by facial unit or subunit allograft transplant. The second goal is to investigate and optimize the surgical aspects of the procedure, including tissue recovery, procurement, and functional outcomes. A third goal is to investigate the immunologic questions related to human leukocyte antigen matching on graft rejection. Finally, with adequate follow-up, we will analyze the quality of life and cost-effectiveness of facial transplantation.

ESTABLISHMENT OF A PROTOCOL

A surgical facial composite tissue allotransplantation protocol was established to formalize three processes: (1) the identification and evaluation of a potential recipient; (2) the identification of a potential donor and appropriate methodology for obtaining consent; and finally, (3) an algorithm for the harvesting and transplantation of the donor allograft to the recipient.

Recipients had to demonstrate severe facial disfigurement, defined as complete loss of a facial unit comprising at least 25 percent of the facial surface, loss of an important facial part, and having anatomically difficult defects to reconstruct with conventional techniques. We only chose recipients who lived within 4 hours of commercial flight time to Boston. Patients had to be 18 years of age or older. Exclusion criteria included a history of a psychiatric illness being actively treated

Disclosure: *The authors have no financial disclosures regarding this article.*

with medications. In addition, enrollment of pregnant women was postponed until 6 weeks following completion of their pregnancy.

Eligible patients were initially evaluated by the primary investigator and then a panel consisting of plastic, oral maxillofacial, and head and neck oncology surgeons. A multiteam approach was undertaken to further evaluate the recipient.

A social worker investigated the patient's history of alcohol/drug abuse, emotional problems and stress management, medical compliance, coordination of benefits, dental health, disability income programs, family medical leave act, health care proxy, medication coverage, and psychological services.

A psychiatric team, specializing in patients with facial deformities, evaluated for history of psychoses, depression, active substance abuse, severe personality disorder, expectations of family members and their ability to provide support, and body dysmorphic disorder. To ensure patients' personal interests, a patient advocate was identified to act on the patient's behalf.

General health screening of the patient included laboratory work (complete chemistry screen, fasting lipids, renal panel, liver function test, parathyroid hormone, complete blood count, prothrombin time/partial thromboplastin time/international normalized ratio, prostate-specific antigen, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, cytomegalovirus, immunoglobulin G, Varicella zoster virus, rapid plasma reagin, and human immunodeficiency virus). Maxillofacial computed tomography with three-dimensional formatting, chest radiography, head and neck computed tomography angiography, and echocardiography were the requisite imaging studies. Other tests included a cardiac stress test, colonoscopy, stool Hemoccult (Beckman Coulter, Brea, Calif.), and purified protein derivative. Female candidates underwent Pap tests and mammograms. Tissue typing, ABO blood group, human leukocyte antigen typing, and panel reactive antibody testing were completed. Immunization requirements included hepatitis B vaccine if the patient was surface antibody–negative, a tetanus shot within the past 10 years, a pneumovax shot within the past 5 years, and a yearly flu shot.

Finally, the patient was brought back for informed consent, which was overseen by the institutional review board. In our informed consent process, the patient is made aware of the current practices for treating facial deformities and the reasons for considering facial composite tissue allotransplantation. Second, comprehension of transplant-specific considerations, including lifelong immunosuppression and possible facial allograft failure resulting in a worse functional and cosmetic outcome and death, was emphasized. The patient consulted with an independent patient advocate to assure complete understanding. The patient was then added to the transplant waiting list, which is held by the principal investigator and New England Organ Bank.

Initial donor selection was led by the organ bank team. Donor families were approached when a diagnosis of brain death was made and the potential donor had previously indicated a willingness for organ donation (based on Registry of Motor Vehicles information). If a family agreed to the donation of organs, tissue donation was queried. If affirmative responses were obtained, facial part recovery was discussed. A separate consent form was developed by the legal department of New England Organ Bank for donation of the facial tissues. Once signed, the lead surgeon was informed about the availability of a matching donor. Given the unique circumstances of facial tissue recovery, the distance from the donor hospital to Boston was set to a maximum of 2 hours' driving distance.

Standard compatibility screening was completed, including ABO blood typing, human leukocyte antigen typing, panel reactive antibody testing, and final crossmatch. A positive T-cell and B-cell crossmatch assessed by cytotoxicity is a contraindication to transplantation. Only heart-beating donors were considered, to maximize the chance of timely transplantation and reduce the risk of ischemic injury to the transplanted graft. Special consideration was given to match sex, skin color, and texture from the donor. The ideal donor age is between 20 years younger and 10 years older than the recipient, though individual considerations are taken into account.[8]

Six experienced microsurgeons, a team of anesthesiologists, and selected operating room nursing staff and technicians were organized. The involved staff was educated on an algorithm of events and procedures and underwent regularly scheduled review sessions. The anatomical details of both procedures were planned in advance by the involved surgeons. Basic tenets of the transplant process included identification of a suitable donor by the lead surgeon, simultaneous dissections of the donor and recipient to minimize the ischemic time of the facial allograft, keeping donor perfusing vessels attached until vascular anastomosis locations are deter-

mined, and a predictable sequence of reattachment (vascular anastomoses followed by deep neurorrhaphies, bony attachment, facial muscle reapproximation, superficial neurorrhaphies, and dermal closure).

IDENTIFICATION OF A RECIPIENT

A 60-year-old man presented to our institution 4 years earlier after falling onto a third rail and suffering fourth-degree burns to the face (Fig. 1). Débridement included excision of his entire external nasal structure, bilateral cheeks, upper lip, palate (including all dentition of the maxilla), all muscles of animation, nasal bones, inferior anterior maxilla, and right inferior orbital floor. The patient's extensive midface defect was covered with a free anterior lateral thigh flap. The patient was deemed legally blind in the right eye (Fig. 2).

Initial third-degree burns to the patient's left lower and right upper extremity were débrided and grafted accordingly. He had developed a claw hand of the right upper extremity with no nerve function and underwent appropriate tendon transfers. Function of his right hand was further limited by a first web space contracture.

The patient's history was notable for hepatitis C infection, with stable viral loads previously managed on alpha-interferon and ribivirin, cerebral aneurysm clipping with a ventricu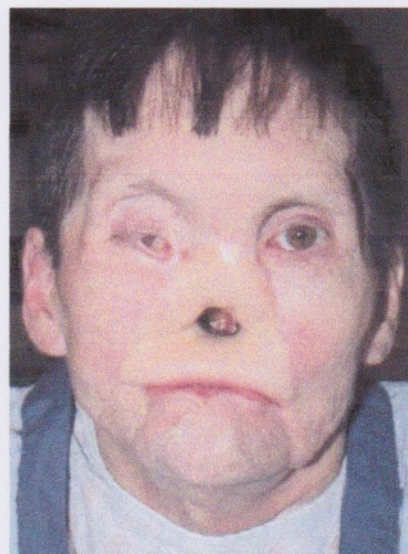loperitoneal shunt for hydrocephalus, splenectomy, and a history of intravenous drug abuse. He was managed with methadone at home. During follow-up with our service before transplantation, the patient was treated with isoniazid therapy for a positive purified protein derivative. Socially, the patient acknowledged a smoking history of 10 pack years but had quit from the time of injury. The patient was a military veteran whose primary social supports included his wife and daughter.

Fig. 2. Recipient after coverage of defect with a free anterior lateral thigh flap with creation of a nasal ostium.

Fig. 1. Recipient at time of initial injury, in 2005, after falling onto a third rail.

SURGICAL PREPARATION FOR COMPOSITE TISSUE ALLOTRANSPLANTATION

Surgical rehearsals were performed along with our French collaborators, Drs. Dubernard, Deveauchelle, and Lengele.[9] Anatomic dissections of the deep and superficial collateral networks of the facial artery revealed important considerations. First, based on midline faciomaxillary shunts between the superior labial artery and distal branches of the sphenopalatine arteries, we believed that an adequate retrograde vascular supply of the hard palate was possible based on the facial artery alone. In contrast, the deep compartments of the cheeks, including the masticatory muscles and Bichat's fat pad, were solely supplied by the terminal branches of the maxillary artery and therefore would not be included in the harvest.

Nerve dissections also revealed important anticipatory steps. Namely, for sensation, an extended supraperiosteal dissection of the orbital floor allows harvest of the infraorbital nerve close to the foramen rotundum, facilitating anastomosis. In contrast, the anatomy of the greater palatine and lesser palatine nerves does not allow adequate anastomosis and therefore was not considered at the time of transplant.[10]

THE TRANSPLANT

The donor was a 60-year-old man with a familial history of dilated cardiomyopathy who had undergone placement of a left ventricular assist device 16 months earlier. His postoperative course was notable for heparin-induced thrombocytopenia. He was admitted to Brigham and Women's Hospital and underwent an orthotopic heart transplant complicated by massive bilateral embolic strokes. The only immunosuppressive therapy the patient had received up to the time of brain death was Solu-Medrol (Pfizer, Inc., New York, N.Y.).

The patient's family gave consent separately for solid organ and composite tissue allograft donation. The consent for donation of facial tissue underscored multiple points: (1) permission to harvest soft tissue and skeletal structures of the face; (2) confirmation of the family's desire for a closed casket funeral; (3) understanding that the acquired facial defect would be covered with a silicone mask of similar skin color; and (4) anticipated media attention, with inevitable identification of both donor and recipient.

The donor's blood type was O-positive, and human leukocyte antigen crossmatch between donor and recipient yielded four loci mismatches and two matches at A3 and DR4. The donor tested positive for immunoglobulin-G antibodies to cytomegalovirus.

The donor and recipient were brought to the operating room simultaneously. The donor dissection began with an outer incision extending superiorly around the glabella, laterally along the junction between the cheek and lower eyelids, and continuing along the lateral cheek area to the upper neck. Medial incisions included the lateral aspect of the lower lip bilaterally and the lower part of the nasolabial folds. The facial vessels were identified and isolated at the mandibular margin.

Communication with the recipient surgical team at this point indicated that the external carotid arteries would be the most suitable site for anastomosis. As the facial vessels were firmly adherent to the underside of the mandible, exposure was facilitated with mandibular osteotomies. Of note, the external carotid arteries were dissected superiorly to above the site of the facial artery take-off and then ligated to reduce bleeding when the final osteotomies were made.

Superficially, the parotid ducts were ligated and reflected medially. Branches of the facial nerve were identified. Exposure of the buccal nerve was facilitated by dissection of the buccal fat pads. The nerves were sequentially identified, tagged, and reflected medially. Mucosal incisions were made through the buccal mucosa proceeding to the maxillary tuberosity in a manner to include both commissures and modioli with the composite allograft.

The zygomatic arch, frontal bone, and infraorbital rims were exposed with periosteal elevators. Osteotomies were performed through the nasal bone centrally, along the floor of the orbits, and then through the zygomatic arches on either side. Posteriorly, osteotomies were performed through the junction of the maxillary bone and pterygoid plates. The thin bone of the orbital floor was ronguered away to identify the infraorbital nerves, which were marked and transected as far back as possible. Osteotomies were then performed in the ethmoid region and along the nasal septum.

When the recipient dissection was complete, the donor's left external carotid and common facial vein were ligated. Given the donor's history of hypercoaguability, the vein was ligated, and the graft was perfused with Wisconsin solution and cooled with ice. The arteries were flushed until clear effluent appeared and tissue plasminogen activator was injected into each of the carotid arteries.

At the completion of the harvest, a silicone mask was fashioned for the facial defect based on a mold obtained before recovery of the facial graft. During the facial composite tissue allograft harvest, a sentinel right radial forearm graft was simultaneously obtained from the upper-right extremity. The donor site was closed primarily.

The recipient dissection began with a skin incision two fingerbreadths below the angle of the mandible along the natural skin creases of the neck. The platysma was divided, and the vessels were exposed. Specifically, the external and internal jugular and facial veins were dissected.

The anterior lateral thigh flap was then removed from the midface. Five branches of the right and left facial nerves were identified and tagged. Subcutaneous tunnels were created above the platysma for the donor vessels. Remnants of the maxilla and portions of the pterygoid plates were resected. Simultaneously, a second surgical team was preparing the patient's right hand for a sentinel graft, which was to serve the dual purpose of rejection monitoring and functional reconstruction of a first web space contracture.

With preparation of the recipient facial bed and harvesting of the composite tissue allograft from the donor complete, as previously described, the allograft was brought into the recipient's operating room. Initially, the soft tissue from the allograft was loosely tacked to the recipient's soft tissue. The donor vessels were passed through the previously formed subcutaneous tunnels into the neck.

Under the microscope, the external carotid arteries and retromandibular veins were prepared on both the graft and recipient. The first anastomosis was performed between the left external carotid arteries. A wave of perfusion crossed the midline of the graft within 20 seconds after release of our arterial clamps. Total ischemia time to the allograft was 1 hour and 15 minutes. The left facial vein and right-sided vessels were similarly joined. During the soft-tissue and skeletal inset, concern with a right external carotid artery clot required a revision of this anastomosis. The right facial arteries were utilized and anastomosed.

To facilitate bone apposition, the donor's nasal, zygomatic, and orbital floor bones were ronguered. Alignment of the skeletons was verified with approximation of the maxillary bone, pterygoid plates, and infraorbital rims. The skeleton was then fixated using plates and screws. The recipient's midline frontal bone was burred down to the donor nasion to maximize bone apposition.

Plate fixation was then performed at the nasion and zygomatic bodies.

Multiple nerve repairs were performed, including those between the infraorbital nerves. Overall, five facial nerve branches were reanastomosed on either side, including the buccal nerve bilaterally.

Intraoral soft tissues were repaired for closure of the graft palatal mucosa to the soft palate of the recipient and then across the buccal mucosa to the oral commissures. The flap was subsequently inset with resection of native skin as needed for tailoring.

The sentinel radial forearm graft from the donor was simultaneously inset into the previously prepared right first web space defect. A percutaneous endoscopic gastrostomy tube was placed at the end of the operation. Total time in the operating room was 19 hours.

The patient was administered CellCept (Genentech, South San Francisco, Calif.) preoperatively and Solu-Medrol and thymoglobulin before reperfusion of the graft. Vancomycin was infused at induction. The patient received 5 units of packed red blood cells during the case.

POSTOPERATIVE MANAGEMENT

The patient's immunosuppressive regimen consisted of 1.5 mg/kg of thymoglobulin daily for the first 4 days postoperatively, 1 g of CellCept twice a day, a Solu-Medrol taper from 100 mg twice a day to 60 mg twice a day over 5 days with transition to prednisone on day 5, and 2 mg of tacrolimus twice a day.

The patient was transferred to the intensive care unit for flap monitoring. Hourly Doppler monitoring and continuous ViOptix monitoring (Fremont, Calif.) were maintained for 4 days. The head of bed was kept elevated to facilitate venous outflow. The patient was given nothing by mouth except for medications. Nutritional supplementation was initiated on postoperative day 1 by tube feedings. The patient's pain was controlled with methadone and oxycodone. The ventilator was removed on postoperative day 2. The patient was transferred to a private room on postoperative day 4. Anticoagulation was maintained with a daily aspirin and early ambulation only. Our usual protocol would have included subcutaneous heparin; however, given the donor's heparin-induced thrombocytopenia history, this drug was withheld. Normal renal function was maintained throughout the admission.

The patient was administered gancyclovir for 5 days, followed by Valcyte (Genentech) daily. Per-

tinent bacterial cultures included extended spectrum beta lactamase–resistant *Escherichia coli* in the donor's sputum. The patient was initially maintained on vancomycin, imipenem, Bactrim (AR Scientific, Inc., Philadelphia, Pa.), and micafungin. When the recipient's intraoperative bronchoalveolar lavage grew methicillin-resistant *Staphylococcus aureus*, azithromycin was added to the regimen. Ultimately, the patient was discharged on 4 weeks of cefepime and Bactrim. Hepatitis C viral loads were monitored and stable throughout this admission. Isoniazid and pyridoxine were continued for 3 months.

The patient was discharged to a rehabilitation facility on postoperative day 13. After discharge, he was monitored with biweekly laboratory work, including tacrolimus levels, complete blood count, complete chemistry screen, and liver function tests weekly. Hepatitis C viral loads were rechecked at 1 month after discharge (Fig. 3).

The patient underwent two revisions of the composite tissue allograft for excision of excess skin and, during the second procedure, local flap closure of a right medial canthal fistula. Currently, 20 months after transplantation, the patient has required seven readmissions, all of which occurred in the first 6 months after transplantation. The first three admissions were for concerns of facial erythema and swelling and possible rejection. During each admission, the patient was successfully treated with pulse dose steroids

and prednisone taper. During the third admission, dermatology evaluation unveiled a history of rosacea, and the erythema was treated successfully with Metrogel (Galderma, Princeton, N.J.). The patient was subsequently readmitted two consecutive times for elective procedures, including a liver biopsy. Five months after the transplant, the patient was admitted for his only episode of flap cellulitis, which was successfully treated with broad-spectrum antibiotics, including vancomycin, cefepime, and clindamycin. Another admission, 6 months after the transplant, was for altered mental status related to an accidental medication overdose.

The patient underwent weekly biopsies of the face and sentinel grafts for the first 3 months and then monthly biopsies until 6 months after transplantation, followed by a 1-year follow-up biopsy. Biopsies consisted of 2-mm punch biopsies from the face and hand. Face biopsy results for the first 6 months consistently demonstrated perivascular chronic inflammation with foci of lymphocytic vasculitis consistent with grade I to early grade II rejection. Hand biopsy results were often nonspecific or demonstrated early mild rejection. The patient's 6-month follow-up face biopsy demonstrated similar results as those reported previously. At 1 year, the face biopsy continued to reveal superficial perivascular lymphocytic infiltrate with follicular infundibular component, which the dermatopathologists were unable to definitely differentiate between mild rejection versus sequelae of the rosacea.

The patient's facial erythema continued intermittently to date and was more likely secondary to rosacea than rejection. The facial edema persisted for approximately 6 months after transplantation and then completely subsided.

FOLLOW-UP

Today, the patient is transitioning back into society. He currently has two roommates and is noted by multiple physicians to be in good spirits. He is also noted to present himself in a clean and groomed manner. The patient views himself positively (Fig. 4).

Neurologic assessment of the graft reveals the ability to smile symmetrically but weakly. The patient subjectively notes that his smile is getting stronger. The patient is unable to puff his cheeks on either side. Jaw opening and tongue strength are completely preserved. Subjectively, the patient continues to note numbness and tingling of the allograft though this continues to improve. Sensory examinations reveal inconsistent results for

Fig. 3. The recipient is shown 1 month after facial composite tissue allotransplantation.

Fig. 4. Recipient is shown 18 months after facial composite tissue allotransplantation.

two-point discrimination, light touch, and temperature bilaterally over the V2 distribution ranging from hyperpathia (150 percent) to diminished sensation (75 percent). The V1 and V3 distributions remain completely intact. The patient's dysarthria is noted to be gradually improving.

FUTURE

During our first case, we learned several important lessons for future work. Life-saving organ recovery is of utmost importance and should not be jeopardized at any point by excessive bleeding causing instability of the donor. Especially in cases in which bone needs to be involved, osteotomies can be dangerous due to potential injury to the pterygoid plexus or arteries in osseous canals that would be impossible to control. We therefore performed a thorough dissection of the common carotids to adequately control for bleeding, should it occur during osteotomy.

Given the unpredictability of which vessels may ultimately be chosen for vascular anastomosis, communication is critical. Selection of vessels before recovery, however, would be ideal. We have learned that vessel selection may not be preoperatively obvious and that changes occur despite adequate preoperative planning. By creating an algorithm of vessel selection, we can simplify and streamline this process.

We have also come to appreciate the importance of recipient computed tomography angiography to identify terminal branches of the external carotid artery, such as the lingual artery or anomalous ophthalmic artery. The angiosomes of these vessels do not always have an adequate back-up collateral system. Therefore, an anastomosis proximal to their take-off can theoretically lead to oropharyngeal or ocular necrosis.

We used a sentinel flap for monitoring rejection to avoid frequent facial biopsies. This monitoring technique did not prove to undergo rejection that correlated to the facial graft. We therefore do not plan to use this sentinel flap in the future. Although biopsies are the definitive standard and will need to be performed in the future as a part of the protocol, better monitoring tools are needed. We are considering the use of laser Doppler as a tool to quantify changes in perfusion and resulting redness in the most superficial layer of skin.

The future of face transplantation is exciting. To date, 18 face transplantations are known to have occurred in the world. Early results show tremendous potential in demonstrating facial composite tissue allotransplantation as a superior option for facial reconstruction of complex facial defects.

As more experience is gained, it is important that protocols and techniques are advanced in a scientific manner. Facial transplantation adds a new dimension of complexity beyond the technical and physiologic demands of the transplant itself. Face transplantation introduces real issues regarding identity, ability to express emotion, and social integration. As we remain in the infancy of this field, we must continue to be vigilant and aware of our response to these concerns to ensure that these procedures are viewed not as scientific experiments but more so as thoughtful, highly technical, and specialized procedures that merge science and art to deliver a powerful surgical solution to the age-old problem of reconstruction for complex facial defects.

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PATIENT CONSENT

The patient provided written consent for the use of his image.

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