ORIGINAL ARTICLE

Outcomes 18 Months after the First Human Partial Face Transplantation

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ABSTRACT

BACKGROUND

We performed the first human partial face allograft on November 27, 2005. Here we report outcomes up to 18 months after transplantation.

METHODS

The postsurgical induction immunosuppression protocol included thymoglobulins combined with tacrolimus, mycophenolate mofetil, and prednisone. Donor hematopoietic stem cells were infused on postoperative days 4 and 11. Sequential biopsy specimens were taken from a sentinel skin graft, the facial skin, and the oral mucosa. Functional progress was assessed by tests of sensory and motor function performed monthly. Psychological support was provided before and after transplantation.

RESULTS

Sensitivity to light touch, as assessed with the use of static monofilaments, and sensitivity to heat and cold had returned to normal at 6 months after transplantation. Motor recovery was slower, and labial contact allowing complete mouth closure was achieved at 10 months. Psychological acceptance of the graft progressed as function improved. Rejection episodes occurred on days 18 and 214 after transplantation and were reversed. A decrease in inulin clearance led to a change in immunosuppressive regimen from tacrolimus to sirolimus at 14 months. Extracorporeal photochemotherapy was introduced at 10 months to prevent recurrence of rejection. There have been no subsequent rejection episodes. At 18 months, the patient is satisfied with the aesthetic result.

CONCLUSIONS

In this patient who underwent the first partial face transplantation, the functional and aesthetic results 18 months after transplantation are satisfactory.

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During the past decade, composite tissue allografts have inaugurated a new era in human transplantation. Allografts of the knee joint,[1] one hand,[2] the larynx,[3] both hands,[4] the abdominal wall,[5] and even the penis[6] have been successively reported. Most were performed in patients with severe defects of nonvital parts of the body that could not be repaired with satisfactory functional and aesthetic results by conventional surgery.

We previously reported the initial results[7] of a partial face transplantation that we performed in a woman who was disfigured by a severe dog bite and in whom conventional reconstruction was considered a poor option. Previous experiments in animals[8] had demonstrated the feasibility of face transplantation, but it had not been performed in humans. Challenges included surgical considerations (determination of how to achieve the best aesthetic and functional results), immunologic questions (identification of a suitable immunosuppressive protocol for preventing and reversing rejection of a composite graft that included the skin), and psychological considerations (assessment of a person's ability to live with a face that is neither her own nor the donor's).

A report published soon after the graft was performed[7] described in detail the anatomic consequences of the dog bite, preparation of the patient for the graft, and the surgical technique used, as well as the initial immunosuppression protocol and the patient's clinical evolution. The present report focuses on the follow-up and clinical evolution during the first 18 months after transplantation.

PATIENT AND METHODS

PATIENT

The recipient, a 38-year-old woman, had been severely bitten by her dog on May 28, 2005, resulting in amputation of her distal nose, her upper and lower lips, her entire chin, and the adjacent parts of her right and left cheeks. The face graft was performed on November 27, 2005, in Amiens, France. The donor, a brain-dead 46-year-old woman, and the recipient had the same blood group (O+) and shared five HLA antigens.

The approval of the local Protection of Persons Committee, the French Agency for Health Safety, and the French Biomedicine Agency was obtained, and the patient signed a detailed informed-consent form before undergoing transplantation. The patient was evaluated preoperatively by three psychiatrists, including one whom she had seen regularly before undergoing transplantation and two others who were involved in the care of recipients of hand transplants; these three psychiatrists also assessed her psychological status after transplantation. The patient was transferred to Edouard Herriot Hospital in Lyon on November 30 for 6 weeks and was followed thereafter both in Amiens and in Lyon.

SURGICAL PROCEDURE

The procedure has previously been described in detail[7] and is shown schematically in Figure 1. In addition to the face transplant, a conventional radial forearm flap was recovered from the donor for transplantation in the recipient's left submammary fold and was used as a sentinel graft for skin biopsies to limit damage to the grafted face.

The immunosuppressive induction protocol included intravenous antithymocyte globulin (Thymoglobulin, Genzyme) for 10 days, oral tacrolimus (target trough levels, 10 to 15 ng per milliliter throughout the first month), mycophenolate mofetil (2 g per day), and prednisone (250 mg on day 1, 100 mg on day 2, and 60 mg per day through day 12, followed by a gradual taper). Medications were also given for prophylaxis of cytomegalovirus infection and *Pneumocystis jiroveci* pneumonia.[7]

HEMATOPOIETIC STEM-CELL TRANSPLANTATION

Before surgery, bone marrow was collected from the donor's iliac crests. After 1724 ml of bone marrow had been harvested, 2.43×10^{10} nucleated cells (4.64×10^{8} per kilogram of body weight), 0.42×10^{6} CD34+ cells per kilogram, and 7×10^{4} granulocyte–macrophage colony-forming units (CFU-GM) per kilogram were obtained. The bone marrow cells were stored in two equal portions in nitrogen gas.

In consistency with the Miami protocol used in cotransplantation of renal and bone marrow cells,[9] half of the bone marrow cells were infused into the recipient on days 4 and 11 after face allotransplantation. The number of viable infused CD34+ cells was 0.12×10^{6} per kilogram on day 4 and 0.10×10^{6} per kilogram on day 11; the number of infused CFU-GM was 2×10^{4} per kilogram on day 4 and 4×10^{4} per kilogram on day 11. Chimerism was assessed on whole blood and on CD3+ and CD56+ cells at days 8, 14, 26, 39, 53, 69, 88, 124, 174, 330, and 545 after transplantation, and on total and purified CD34+ bone mar-

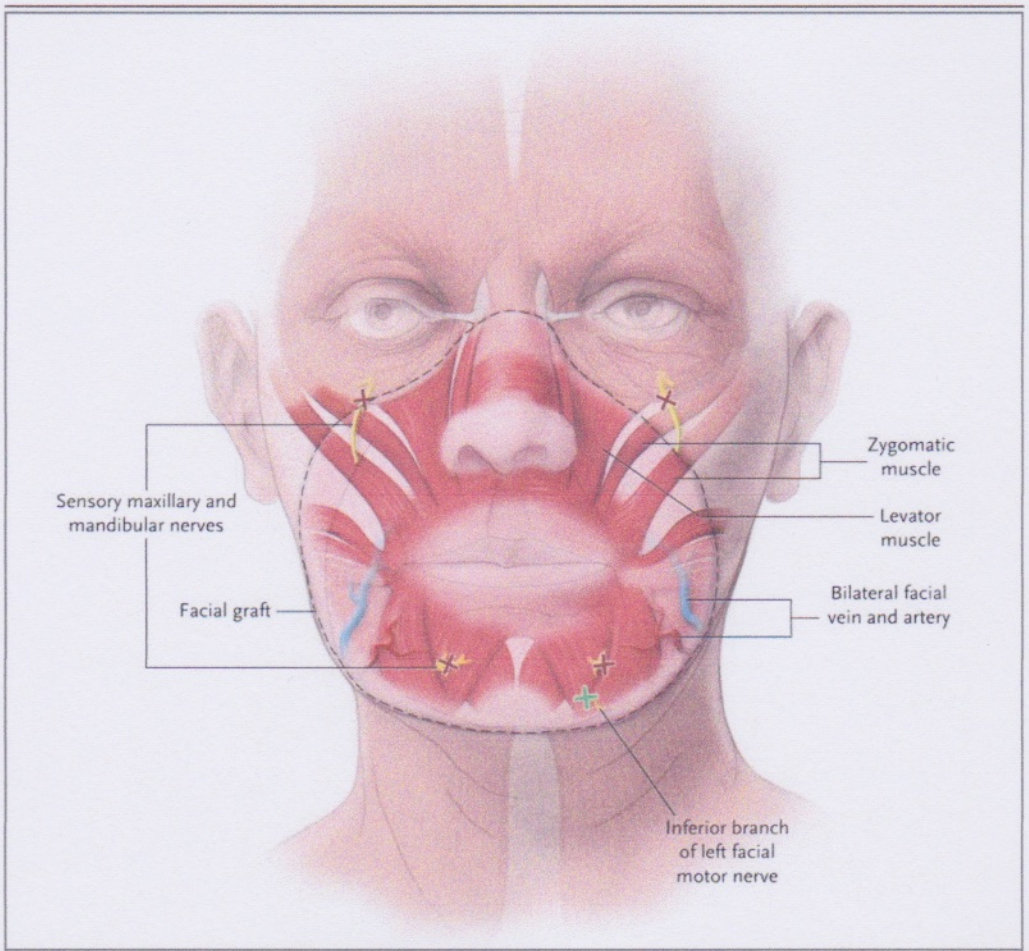


Figure 1. Schematic Representation of the Surgical Procedure.

The figure shows vascular anastomoses of the bilateral facial arteries (red) and veins (blue); sutures of the sensory maxillary (V2) and mandibular (V3) nerves (yellow) and the inferior branch of the left facial motor nerve (green cross); and musculomuscular sutures on the levator and zygomatic muscles.

row cells at days 14, 26, 53, 90, 174, 370, and 545. Chimerism was determined by real-time quantitative polymerase chain reaction (RQ-PCR)[10] with the use of TaqMan technology and an ABI 7700 Sequence Detector (Applera). The lower limit of the assay was 0.1%. Microchimerism was defined by the presence of 1% donor cells or less.

Extracorporeal photochemotherapy was initiated in late August 2006. It was performed, as described elsewhere,[11] twice a week for 4 weeks, once a week for 8 weeks, once every 2 weeks for 2 months, and then once every 4 weeks for the duration of the 18-month follow-up period.

Mucosa and skin biopsies of the cheek and the sentinel skin graft were performed at the time of rejection episodes and systematically every week for 1 month, monthly for 4 months, and every 6 months thereafter. To minimize the risk of scarring, only a small number of biopsies were performed on the face graft itself, and these were done only to evaluate rejection episodes. Effector T cells were isolated from sentinel skin graft biopsy specimens and cultured for 2 weeks with 20 IU of human interleukin-2 per milliliter. Cytotoxicity was measured by the standard chromium-release assay. ^{51}Cr-labeled type B Epstein–Barr virus lymphoblastoid cell lines generated from the donor, the recipient, or a third-party healthy blood donor who was fully mismatched with both the donor and the recipient were used as targets.

Physical therapy was started 48 hours after

surgery and was performed twice daily for the first 4 months and once daily thereafter. The rehabilitation program involved training in passive and active facial exercises, which were mainly focused on the restoration of lip movement and mouth occlusion.

Psychological support was provided once daily during the first 4 postoperative weeks, twice weekly for the next 4 months, and then once a month or at the patient's request.

RESULTS

FUNCTIONAL RESULTS

The patient was able to eat and drink almost normally by the end of the first postoperative week, although leakage of her drinks from her mouth was sometimes observed; this disappeared completely by 12 months. At 8 months, she was operated on for an unexplained stenosis of the duct of Steno, and the outcome was favorable.

As assessed by repeated Semmes–Weinstein tests (light touch sensation studied by using static monofilaments), sensory discrimination was recovered quickly (Fig. 2A). Sensory discrimination was present on the lateral part of the upper lip and the lateral area of the chin and lower lip on both sides after 10 weeks and thereafter involved the whole skin surface of the face transplant, as well as the grafted oral mucosa. Heat and cold sensation was nearly normal at 4 months and normal at 6 months over the entire graft (Fig. 2B). No contact hyperesthesia was observed.

Motor recovery was slower than sensory recovery. The patient had some ability to move the upper lip by the 12th postoperative week. Motion of the lower lip recovered progressively from the fourth postoperative month. Since the third month after transplantation, improvement of lip closure has greatly facilitated the pronunciation of phonemes such as P and B (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org, for a video demonstrating the patient's facial-muscle function). Complete labial contact was present at 6 months (Fig. 3A and 3B). Endobuccal pressure (assessed with the use of an endobuccal balloon connected to a pressure monitor) increased progressively, reflecting improved cheek-muscle strength. Contractions of the chin muscles and the nose pyramidal muscles were present at 12 months. Phonation and mastication continued to improve, with normal mobilization of the food bolus at 6 months. The smile, which was incomplete at 4 months, remained asymmetric up to the 10th postoperative month but was nearly normal at 14 months and normal at 18 months. These functional improvements are reflected in the emotional expressions on the patient's face, such as when she has feelings of joy or sadness.

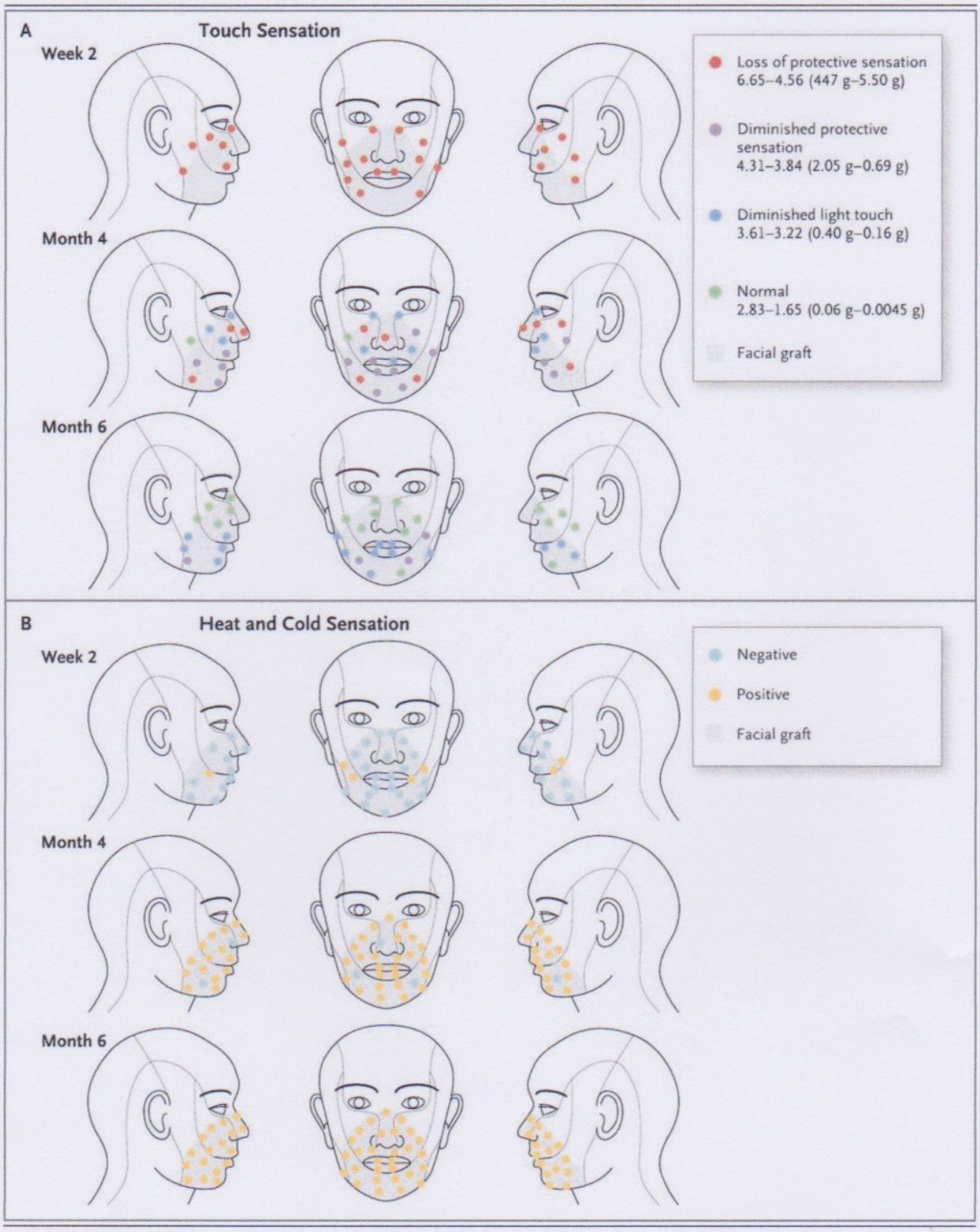
Figure 2 (facing page). Recovery of Sensory Function in the Transplanted Tissue.

Panel A shows recovery of touch sensation, as assessed by the static monofilament (Semmes–Weinstein) test. Panel B shows recovery of heat and cold sensation. The numbers represent the size of the monofilament as designated by the manufacturer and the target force (in grams).

IMMUNOLOGIC OUTCOME

Two episodes of acute rejection occurred on days 18 and 214 post-transplantation. Clinically, they were characterized by the gradual development of erythema and edema on the oral mucosa and on the skin of the face and the sentinel flap (Fig. 4). Rejection was confirmed by biopsies of the skin of the face and the sentinel flap, which disclosed dermal edema, a predominantly lymphocytic inflammatory-cell infiltrate of variable density, epithelial (epidermis or mucous membrane) intracellular edema, lymphocyte exocytosis, basal-cell vacuolization, and keratinocyte apoptosis. Moderate perivascular-cell infiltration was also seen in the grafted derma.[12] These lesions were graded as 1 or 2 (mild and moderate rejection, respectively), according to the classification established for acute rejection of composite tissue.[13] Immunohistochemical studies showed that the lymphocytes were predominantly CD4+ cells, with a few CD8+ cells (data not shown). In support of these results, specific donor-directed cytotoxic activity was observed in T cells isolated from the skin of the sentinel graft on days 36 and 214, but not in those isolated on day 76 (Fig. 5), when clinical and histopathological signs of the first rejection had disappeared.

The first rejection episode was initially treated by increases in the doses of oral prednisone, tacrolimus, and mycophenolate mofetil, as well as clobetasol ointment and prednisone mouthwashes. Subsequently, three 1000-mg boluses of



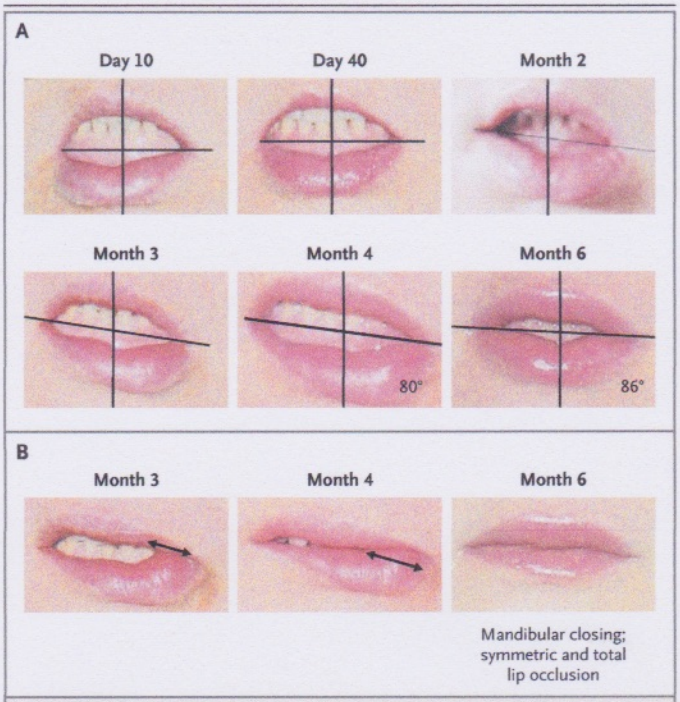


Figure 3. Recovery of Lip Occlusion in the Transplanted Tissue.

Panel A shows recovery of passive lip occlusion, and Panel B recovery of active lip occlusion. Symmetric and total passive and active occlusion were attained at 6 months post-transplantation. The arrows show the consequences on motor recovery of the initial wound asymmetry.

methylprednisolone were administered intravenously, resulting in reversal of the rejection. The mucosa, the graft, and the sentinel flap returned to normal clinically and pathologically by day 45.[7]

The second rejection episode was effectively treated by three 750-mg boluses of methylprednisolone administered intravenously every other day, combined with prednisone mouthwashes and local applications of clobetasol and tacrolimus ointments. Doses of oral corticosteroids were subsequently increased to 50 mg daily (1 mg per kilogram of body weight per day for 10 days) and progressively tapered to 5 mg daily over 8 weeks. The tacrolimus and mycophenolate mofetil doses remained unmodified.

Extracorporeal photochemotherapy was started 2 months after the second rejection episode in an effort to reduce the risk of further episodes of acute rejection, and this therapy has been well tolerated. Since September 2006, the appearance of the facial skin, the sentinel skin, and the oral graft mucosa has been normal. No graft-versus-host disease (GVHD) has developed.

POST-TRANSPLANTATION CHIMERISM

Of the many assessments for microchimerism, only one suggested that microchimerism was present. This assessment occurred 2 months after transplantation, when RQ-PCR study showed 0.1% donor cells among the CD34+-enriched population of bone marrow cells.

INFECTIOUS COMPLICATIONS

Two infectious complications occurred. On day 185, a type 1 human herpes simplex virus infection of the lips was confirmed by virologic testing and was treated effectively with oral valacyclovir and topical acyclovir cream. A few days after reversal of the second rejection episode, molluscum contagiosum due to poxvirus appeared over the cheeks on both the allograft and the patient's own skin and was treated by curettage.

OTHER POST-TRANSPLANTATION COMPLICATIONS

When the patient was on the initial immunosuppressive regimen, she had a progressive decrease in renal function: inulin clearance was 90 ml per minute per 1.73 m^2 of body-surface area before the graft and decreased to 59 and 43 ml per minute per 1.73 m^2 at 6 and 12 months, respectively. The serum creatinine levels were 0.6, 0.9, and 1.5 mg per deciliter (53, 80, and 133 μmol per liter) at baseline, 6 months, and 12 months, respectively. There was no proteinuria. Renal failure was thought to be attributable to tacrolimus, although trough levels ranged from 8 to 10 ng per milliliter and never exceeded 15 ng per milliliter. Sirolimus was introduced 11 months after transplantation with a plan to gradually taper tacrolimus and preclude the nephrotoxicity of calcineurin inhibitors.

Five weeks later, when the tacrolimus and sirolimus trough levels were 4.9 and 3.3 ng per milliliter, respectively, moderate thrombotic microangiopathy developed, characterized by thrombocytopenia (platelet count, 100,000 per cubic millimeter), hemolytic anemia (hemoglobin level, 7.9 g per deciliter) with fragmented erythrocytes, acute renal failure (creatinine increased to 2.2 mg per deciliter [194 μmol per liter]), and hypertension. Tacrolimus and sirolimus were stopped, and fresh frozen plasma was infused for 4 days, combined with a high dose of intravenous immune globulin. Thrombotic microangiopathy resolved within 8 days, and sirolimus was reintroduced 1 week later, when serum creatinine had dimin-

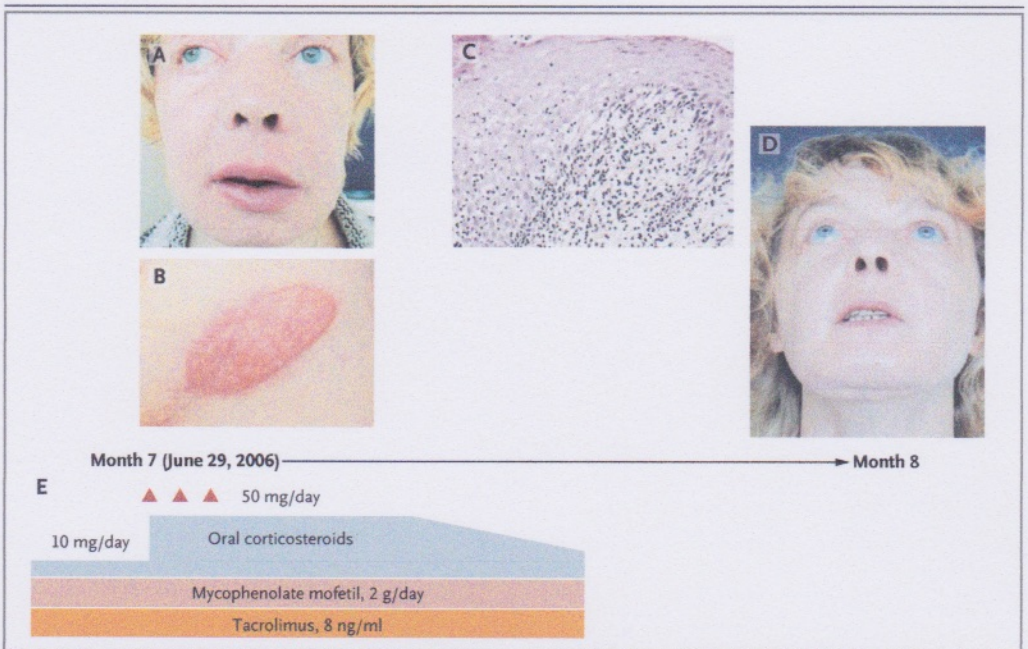


Figure 4. Immunologic Complications during the Second Episode of Acute Rejection of the Facial Graft.
Erythema of the facial graft (Panel A) and submammary sentinel flap (Panel B) with typical dermal infiltration by mononuclear cells (Panel C) is shown. Panel D is a photograph taken at 8 months post-transplantation showing return to normal appearance after three 750-mg boluses of intravenous methylprednisolone. Panel E shows the immunosuppressive treatment of the rejection episode. Arrowheads represent the three boluses of methylprednisolone.

ished to 1.2 mg per deciliter (106 μmol per liter). At the present time, the patient's immunosuppressive regimen includes sirolimus (targeted trough level, 8 to 12 ng per milliliter), mycophenolate mofetil (2 g per day), and prednisone (10 mg per day). No acute rejection has occurred since the immunosuppression regimen was altered. Renal function has improved slowly since the withdrawal of tacrolimus. At 18 months of follow-up, the serum creatinine level was 1.1 mg per deciliter (97 μmol per liter), and the measured creatinine clearance was 71 ml per minute per 1.73 m².

PSYCHOLOGICAL AND AESTHETIC RESULTS

Figure 6 shows the patient's face before her injuries, 1 year after transplantation, and 18 months after transplantation. The patient has not undergone formal psychological testing. By the end of the 12th postoperative week, the patient was capable of facing the outside world and gradually resumed a normal social life. The progressive return of expressiveness correlated well with psychological acceptance of the foreign graft. At present, the patient says she is not afraid of walking in the street or meeting people at a party, and she is very satisfied with the aesthetic and functional results.

DISCUSSION

At follow-up 18 months after face transplantation, the patient is doing well in terms of function of the transplant, social functioning, and her overall condition. Recovery of sensation (although subnormal) at 6 months and of lip mobility at 6 months contributed to the return of an almost normal appearance, and the patient is very satisfied with the results of the transplant.

Despite the presence of only one HLA-DR mismatch between the patient and the donor and the potent induction of immunosuppression, two episodes of rejection occurred; the second may have been triggered by the preceding herpesvirus infection. In contrast to reported rejections after hand transplantation, which were controlled by a moderate increase in the dose of prednisone

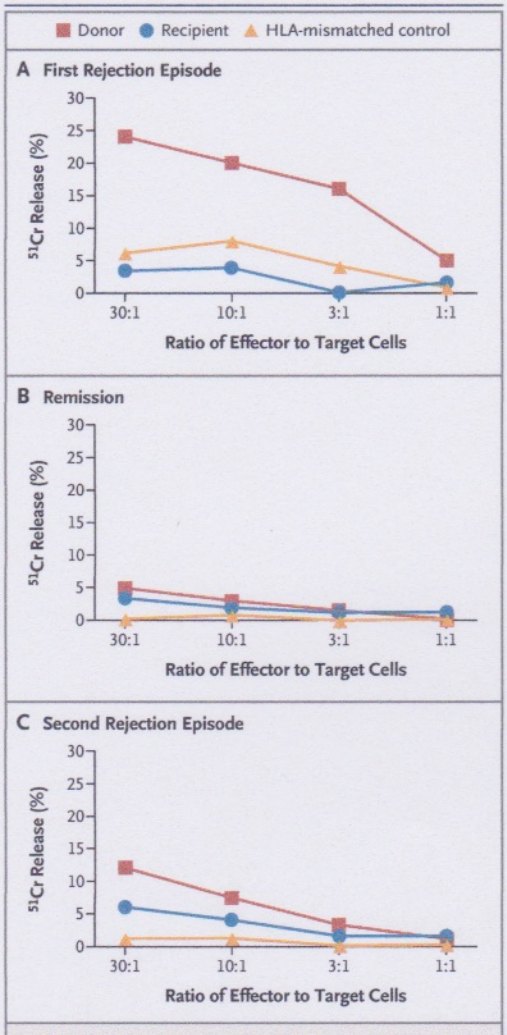


Figure 5. Cytotoxic Activity of T Cells Isolated from the Skin of the Sentinel Graft.

Cytotoxic activity of T cells from the skin of the sentinel graft against ^{51}Cr-labeled type B Epstein–Barr virus lymphoblastoid cells derived from the donor, the recipient, and a third-party, fully HLA-mismatched, healthy blood donor was measured by chromium-release assay on postoperative days 36 (Panel A), 76 (Panel B), and 214 (Panel C).

and by local application of tacrolimus and corticosteroid creams,[14] boluses of injected corticosteroid were necessary to reverse acute skin rejection. Macroscopic changes of the oral mucosa (erythema and edema) appeared 2 days before the first skin-rejection episode, suggesting that mucosal rejection may appear before skin rejection. Biopsies of the sentinel skin flap and donor oral mucosa were useful during the entire 18-month follow-up period for the diagnosis of rejection. The macroscopic features of the sentinel flap corresponded well to those of the facial graft, and the pathologic patterns of rejection were similar when skin-biopsy specimens from both sites were compared. This synchronicity should be confirmed in other patients before sentinel-flap biopsies are used as a reliable marker of face rejection.

Concern about the possibility of irreversible skin rejection led us to use hematopoietic stem-cell infusions. The role of donor hematopoietic stem cells in inducing tolerance of transplanted organs is uncertain. Nevertheless, the clinical results of previous kidney, pancreas, liver, and heart transplantations that included donor bone marrow infusions[9,15-18] have suggested a decrease in the risk of chronic rejection and longer graft survival, without specific complications connected with the procedure. In the cadaveric donor, bone marrow cells have been recovered from the iliac crest; the number of nucleated cells we collected was considered adequate on the basis of reports of tandem bone marrow and kidney transplantation from living, related donors.[19] However, despite the absence of apparent problems during harvesting, cryopreservation, and thawing, the numbers of CFU-GM and viable CD34+ cells for both grafts were smaller than usually observed.

During the 18-month follow-up, microchimerism was demonstrated in only one evaluation of the bone marrow. The relationship between microchimerism and tolerance is still controversial.[20,21] Immunoregulatory effects of donor bone marrow cells on the allogeneic cellular immune response have been shown.[22] The long-term presence of regulatory T lymphocytes after transplantation was shown in a patient of ours who has the oldest hand allograft.[23] It is uncertain whether microchimerism due to the bone marrow transplanted with the hand allograft was necessary to induce this regulatory effect and whether a small number of hematopoietic stem cells ("nanochimerism" or "cryptochimerism") can play a role in "educating" T lymphocyte cell lines at the central or peripheral level. Extracorporeal photochemotherapy, an alternative treatment for corticosteroid-resistant GVHD,[24] has also been used to prevent cardiac rejection.[25] We decided to use it

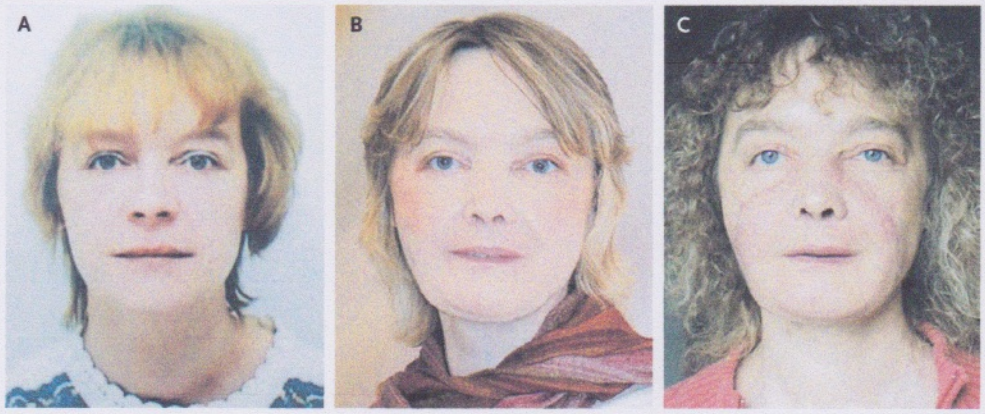


Figure 6. Aesthetic Results.

The photographs were taken in June 2001, 4 years before the dog bite (Panel A); in November 2006, 1 year after transplantation, showing the patient with makeup (Panel B); and in June 2007, 18 months after transplantation, showing the patient without makeup (Panel C).

after the second acute rejection to prevent both acute and chronic rejection without intensifying the immunosuppressive regimen.

Chronic renal failure is a well-known complication of long-term immunosuppressive therapy after organ transplantation. The rapid decline in renal function during the year after transplantation prompted us to switch from tacrolimus to sirolimus, after which renal function improved.

Reports have not yet been published on two other face grafts that were performed in March 2006 in China and in January 2007 in France. More cases will be necessary to allow thorough study of the problems encountered in our patient. Meanwhile, the encouraging 18-month outcomes of face transplantation in our patient suggest that this procedure can offer hope for some patients with severe disfigurement.

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A video showing the patient's facial-muscle function is available with the full text of the article at www.nejm.org.

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