Case Report

Composite Tissue Allograft Transplantation of Cephalocervical Skin Flap and Two Ears

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Malignant melanoma is one of the most aggressive tumors, with an incidence that continues to increase.[1] It is liable to proliferate and metastasize with chemoresistance in a majority of cases. Surgical resection remains the primary treatment for cutaneous malignant melanoma both primary and recurrent if possible. Monochemotherapy with dacarbazine is still the first choice for metastases,[2] because trials have failed to demonstrate significant survival benefit in patients treated with polychemotherapy compared with monochemotherapy or in patients treated with adjuvant immunotherapy or biotherapy compared with chemotherapy.[1,3,4] At present, interferon is the only U.S. Food and Drug Administration–approved adjuvant treatment for high-stage melanoma and has shown indefinite benefits at the price of considerable toxicity[2,5,6]; the optimal dosage and duration of treatment are yet to be defined by ongoing studies.[4,5]

Radical resection will leave extensive tissue defects that are difficult to reconstruct using limited sources of autogenous tissue. Full functional and aesthetic reconstruction is challenging and is only rarely achieved. Although the benefits versus risks of composite tissue allograft transplantation are a matter of debate, most clinicians agree on the goal of making it a clinically feasible treatment that would serve as an ideal source for the replacement or reconstruction of tissues after traumatic loss or tumor resection and for the repair of congenital abnormalities.[7] New advances in immunosuppressive regimens have greatly improved the outcome of composite tissue allograft transplantation. The first human hand allograft transplant was successfully performed and reported in September of 1998,[8] and some other countries have also successfully performed hand allograft transplants.[9,10] The successful experimental model of composite face/scalp flap transplantation in the rat[11] encouraged us to develop a protocol for composite tissue allograft transplantation on a female patient with cutaneous melanoma.

The transplant was designed and performed following the Declaration of Helsinki with the recipient's informed consent. We made a comprehensive pretransplantation evaluation on the patient's general condition and therapeutic efficacy of previous treatment including surgery, chemotherapy, and immunotherapy. We then discussed with the patient the treatment of her tumor. We informed her of the risks and benefits of transplantation surgery and chronic immunosuppression in detail. The patient realized all the risks of infection, rejection, and malignancy with chronic immunosuppression and the benefits of tumor ablation and aesthetic reconstruction.

Case Report

A 72-year-old woman was pathologically diagnosed with cutaneous malignant melanoma on the vertex in October of 2002. She received local resection twice after diagnosis for local spread of the tumor. Continuous chemotherapy and immunotherapy did not halt the tumor spread to the posterior and anterior ear areas, the cervical lateral and adjacent lymph nodes (Fig. 1). The pathologic stage in this patient was American Joint Committee on Cancer Staging System for Cutaneous Melanoma IIIC with thickness greater than 4.0 mm, ulceration, and four positive nodes, and the 5-year survival expectation was less than 25 percent.[12] Therefore, she received extensive radical resection of the huge tumor and autogenous skin flap transplantation in June of 2003. Excised

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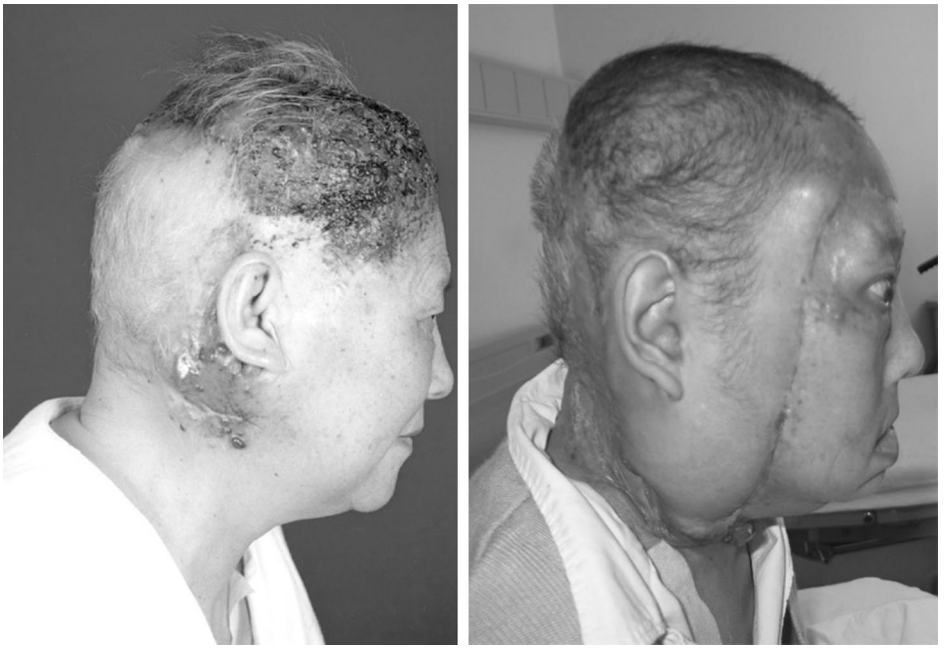

FIG. 1. Comparison of preoperative side elevation (*left*) and postoperative side elevation at day 120 (*right*).

tissues included the scalp, facial/cervical skin, two ears, and adjacent lymph nodes (Fig. 2). The tissue defect was not completely reconstructed by the autograft and left approximately 3 percent of body surface area exposed. There was not enough vascularized autogenous skin flap to repair the tissue defect. Therefore, composite tissue allograft transplantation of cephalocervical skin flap and two ears was designed and performed to facilitate the extensive radical resection, restore the function of the external ear, and complete her cosmetic requirement.

This transplant was performed on September 16, 2003. The panel-reactive antibody assay, the ABO blood group matching, and the cross-match test were performed in choosing an appropriate donor. The recipient received the panel-reactive antibody assay before operation with 0.12 percent of HLA class I and 0.61 percent of HLA class II. A brain-dead young man with the same blood type and a negative cross-match test was selected. A II-shape cut was made on the donor's neck. After exposure of the carotids, the graft was flushed with 1000 ml of 0 to ~4°C University of Wisconsin solution through the carotids.[13] When the solution flowing out from the carotids became pellucid, the composite tissue including the scalp, facial/cervical skin, two ears, and vessels was excised and preserved in 0 to ~4°C University of Wisconsin solution. The total warm ischemia time was limited to 2 minutes. After being excised the graft was sheared and accepted irradiation with a low dose of 8 Gy for 20 minutes. The cold ischemia time was limited to 6 hours.

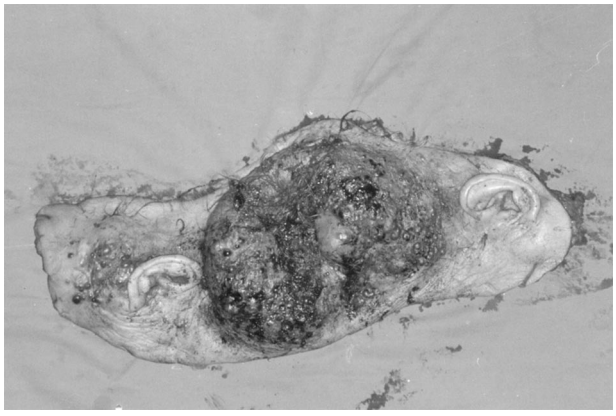

FIG. 2. Excised tissues with tumor inside, including cephalocervical skin and two ears.

Preparation of the recipient area included separating vessels and ablation of the residual melanoma focus. Two ears were anastomosed to external auditory meatus of both sides. After flushing with 4°C plasma, the donor graft was vascularly anastomosed to the recipient. The donor's jugular external arteries were anastomosed to the recipient's left jugular external artery and right thyroid superior artery, and the donor's external jugular veins were anastomosed to the recipient's internal jugular veins, respectively. The donor skin border was then sewn to the recipient site by intermittent suturing. Negative pressure suction was used for drainage at both sides.

Quadruple therapy of tacrolimus, mycophenolate mofetil, steroids, and Zenapax was adopted as immunosuppressive regimen. Tacrolimus was initiated with 3 mg given orally 2 hours before operation, changing to 3 mg twice daily after operation. We precisely adjusted the blood concentration of tacrolimus at 20 to ~25 ng/ml during the first 2 weeks and at 15 to ~20 ng/ml during the next 2 weeks according to laboratory test results. After the first month, it was controlled under 10 ng/ml for maintenance. Methylprednisolone was initiated at 1 g intraoperatively and tapered to 20 mg/day quickly within 1 week after the operation. Thereafter, it was replaced by prednisone given orally at a small dose of 20 mg/day for 3 months and 15 mg/day for 6 months. Mycophenolate mofetil was initiated at 0.75 g 2 hours before the operation and continued at 1.5 g/day postoperatively with no changes for the first 2 months. Zenapax was initiated at 50 mg given soon after anastomosis of vessels and followed by 50 mg

biweekly postoperatively. Postoperative acute rejection was to be treated with high-dose intravenous methylprednisolone and topical tacrolimus. Intravenous infusion of broad-spectrum antibiotics was used for preventing infection during the first 10 days postoperatively and would be used again if necessary.

Clinical signs and symptoms of the patient and the allograft were observed at least four times daily after transplantation. Subsequent biopsies of graft skin were made at 7, 14, 30, and 120 days postoperatively to reveal incipient graft rejection before the appearance of clinically obvious lesions. Blood concentration of tacrolimus was tested frequently and used to direct drug dose adjustments.

The patient's vital signs were stable. Circulation of the allograft was good with normal temperature and elasticity. Primary healing of the skin incision and partial growth of hair were observed postoperatively (Fig. 1). No clinical graft-versus-host disease was noted. Infection was also successfully prevented with the use of broad-spectrum antibiotics. Visceral functions and the blood sugar level were normal. Early ischemia-reperfusion injury of the graft was observed, but it disappeared quickly after the operation. Postoperative biopsies showed that the epidermis of graft skin was integral and moderately keratinized at day 30 and day 120 with a small amount of lymphocyte infiltration in the dermis (Fig. 3) There was no biopsy-confirmed or clinically observed rejection in any episode. Results demonstrated that the immunosuppressive treatments were successful.

DISCUSSION

This patient had cutaneous malignant American Joint Committee on Cancer Staging System for Cutaneous Melanoma stage IIIC melanoma that spread very quickly and caused severe symptoms. Previous chemotherapy and immunotherapy had failed to inhibit proliferation and metastasis of the tumor. There is general agreement that systemic chemotherapy is rarely an effective management of melanoma with regional positive lymph nodes.[14] Surgical resection remained an appropriate choice for this patient because data suggested that patients whose metastases could be completely resected would experience improved overall survival and occasional long-term cure.[15] The Mohs micrographic surgery should first be recommended, particularly in melanomas of the head, neck, and extremities.[16,17] Others found that the Mohs surgery recommended margins were inadequate in some melanomas with large in situ lesions.[17] We had the thick melanoma excised with 5 cm margins plus elective lymph node dissection. The radical resection of the tumor left a large tissue defect that was difficult to reconstruct using a limited source of autogenous skin flap. Composite tissue allograft transplantation offered potential of functional and aesthetic reconstruction.

With advances in surgical techniques and application of new immunosuppressants, organ transplantation comes to be more safe, simple, and effective. Composite tissue allograft transplantation offers a novel therapeutic option to correct untreatable large-tissue defects caused by extensive tumor ablation, trauma, and severe burn. Composite tissue allograft consists of various tissues that express

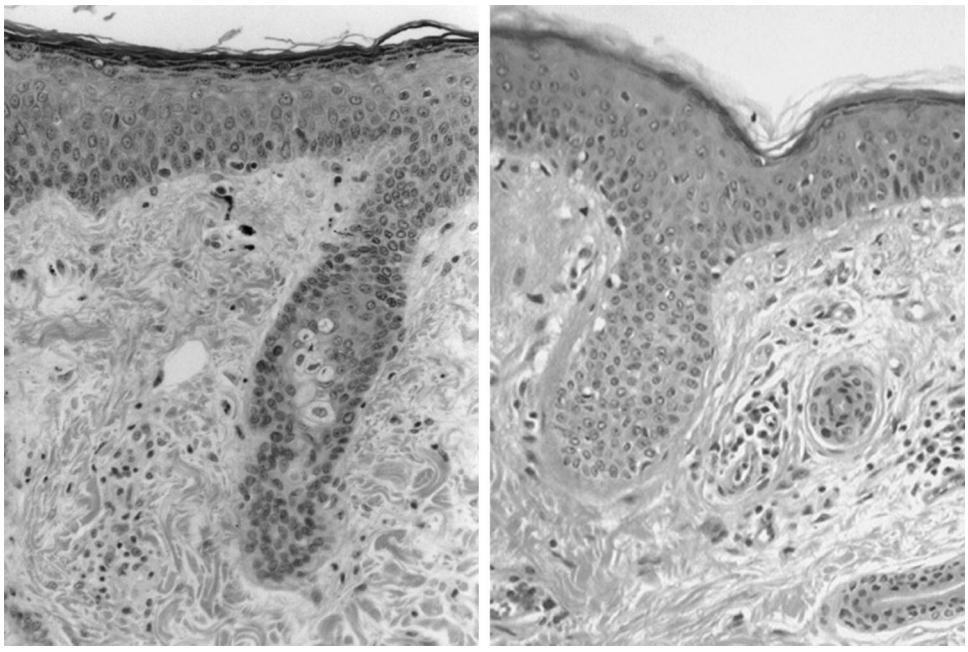

FIG. 3. Postoperative graft skin biopsy specimens at day 30 (*left*) and day 120 (*right*) confirmed that there had been no acute rejection (hematoxylin and eosin stain).

varying degrees of antigenicity[18]; when the skin component is highly antigenic, it makes itself the major target of alloaggression and the obstacle to expanding composite tissue allograft transplantation.[19,20]

Good tissue matching is a prerequisite for successful transplantation and is closely associated with the survival of grafts. Panel-reactive antibody negative and high-grade HLA matching can decrease the ratio of early allograft loss and improve the host/allograft survival rate. The application of genetic matching could allow for the reduction of long-term immunosuppression in composite tissue allograft transplantation.[7] We selected the ABO blood group match, the panel-reactive antibody assay, and the cross-match test, which are often adopted in solid organ transplants. With a highly matched donor, acute rejection was easily prevented in this transplantation.

Irradiation of the graft is a novel immunosuppressive treatment that has been proven to have extended immunosuppressive effects in both experimental and clinical studies on transplants.[9,21–24] Preoperative low-dose irradiation could reduce graft-versus-host disease, prolong graft survival time, and help control acute rejection but not injure endovascular cells or cause artery spasm.[23,25] Selection of radiation dose considered preexisting hand transplant reports that used 8 Gy for 30 minutes, although a shorter duration of 20 minutes was used in this transplant.[9,24,25] Good results of the donor circulation and vitality substantiated the normal function of donor vessels.

Since the 1990s, various new immunosuppressive drugs have significantly improved the clinical efficacy of anti-rejection therapy, such as tacrolimus, mycophenolate mofetil, Zenapax (monoclonal humanized interleukin-2 receptor antibody) (daclizumab; Hoffman-La Roche, Inc., Nutley, N.J.), and rapamycin. Tacrolimus is significantly superior to both cyclosporine and mycophenolate mofetil in composite tissue allograft transplantation.[26] Combination use with tacrolimus and mycophenolate mofetil has allowed composite tissue transplantation to become a predictable clinical reality. These combination regimens permit dose reduction of individual drugs and decrease the risks of infection, malignancies de novo, or recurrence and toxicities and strengthen their anti-rejection capabilities. Contrary to the view that immunosuppressants promote cancer, new data indicate that some of these substances (mycophenolate mofetil and rapamycin) may actually be used to treat cancer.[27–30] Corticosteroids have been used to treat certain types of cancer, such as lymphomas, for many years despite an association with Kaposi sarcoma.[31,32] In our patient, a quadruple immunosuppressive regimen of tacrolimus, mycophenolate mofetil, steroids, and Zenapax was designed after referring to preexisting hand transplant immunosuppressive regimens.[8,9,19] The effects of this immunosuppressive regimen in the overall survival of the patient with melanoma are not known and need to be evaluated in further studies.

Although a successful animal model of composite tissue allograft transplantation without long-term immunosuppression had been documented,[33] there were no human reports. Experimental study demonstrated that continuous immunosuppression was necessary to preserve optimal morphological and functional conditions of allografts.[34] The postoperative dose of tacrolimus was adjusted to maintain the blood concentration at 20 to ~25 ng/ml in the first 2 weeks, at 15 to ~20 ng/ml in the next 2 weeks, at 10 to ~15 ng/ml in the second month, and less than 10 ng/ml thereafter, which was slightly higher than in the hand transplants. Steroids were initiated with 1 g methylprednisolone given intraoperatively and tapered to 20 mg/day quickly after 1 week because steroid withdrawal in the early postoperative period can be particularly advantageous to the recipient of a composite tissue allograft.[35] One week later, methylprednisolone was replaced by prednisone at 20 mg/day for 3 months and 15 mg/day for the next 6 months. Mycophenolate mofetil was used at 1.5 g/day for maintenance with no change during the first 2 months. This regimen based on tacrolimus and mycophenolate mofetil with adjuvant steroids has been widely used and proven to be effective in both solid organ transplantation and composite tissue transplantation.

Early success in composite tissue allograft transplantation of a cephalocervical skin flap and two ears has been achieved as of a 4-month follow-up; longer follow-up is ongoing to evaluate the long-term effects.

Summary

We have achieved early success in composite tissue allograft transplantation in a 72-year-old female patient who had previously undergone radical resection of cutaneous malignant melanoma. We obtained good functional and cos-

metic results. No signs of rejection or tumor recurrence were observed over a 4-month follow-up. Good tissue matching and appropriate immunosuppressive treatment were prerequisites to ensure the survival of the composite tissue allograft. Longer follow-up is needed to determine the long-term effects of this composite tissue allograft transplantation.

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