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CASE REPORT

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Consideration of difficulties and exit strategies in a case of face allotransplantation resulting in failure

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We describe the first rescue procedure in a case of total face allotransplantation. The recipient was a 54-year-old man with severe disfigurement of the entire face following an accidental gunshot injury 5 years previously. The large defect included the maxilla, mandible, and mid-face. Full face procurement was performed from a multiorgan cadaveric donor and was allotransplanted to the recipient. The post-transplant induction immunosuppressive regimen included ATG combined with tacrolimus, mycophenolate mofetil, and prednisone, while maintenance was provided by the last three of these. Although the early postoperative period was uneventful, squamous cell carcinoma developed in the upper and lower extremities in the fifth postoperative month, and post-transplant lymphoproliferative disorder (PTLD) occurred in the sixth month postoperatively. Malignancies were treated, involving both surgical and medical approaches. The patient developed opportunistic pulmonary and cerebellar aspergillosis. In order to reduce the adverse affects and metabolic and immunological load, the transplanted face was removed and replaced with a free flap. Although the early postoperative period was promising, with the transferred flap surviving totally and all vital signs and general status appearing to be improving, the patient was eventually lost due to complicated infectious and metabolic events. Although this case was unsuccessful, we suggest that the immunological and metabolic load should be reduced as soon as stable medical conditions are established in case of diagnosis of a situation involving a high rate of mortality, such as PTLD and untreatable opportunistic infections. This should include withdrawal of all immunosuppressive drugs and removal of all allotransplanted tissues.

1 | INTRODUCTION

Face allotransplantation is an increasingly common restorative procedure aimed at replacing function and esthetic appearance in patients with severe disfigurement which cannot be managed by conventional reconstructive procedures (Brandacher, 2013; Devauchelle et al., 2006; Guo et al. 2008; Lantieri et al., 2008; Meng et al., 2014; Siemionow et al. 2009; Siemionow & Ozturk, 2011; Weissenbacher, Hautz, Pratschke, & Schneeberger, 2013). The most serious attendant handicap is the use of immunosuppressive drugs, which are known to increase the risk of opportunistic infections, metabolic complications, and malignancies (Gordon et al., 2009; Losee, Fletcher, & Gorantla, 2012; Ravindra, Wu, McKinney, Xu, & Ildstad, 2009; Schneeberger et al., 2011). As in all surgical procedures, there must be exit strategies in composite tissue allotransplantations in case of unfavorable developments (Siemionow & Ozturk, 2012). Considerably more experience has been accumulated with solid organ transplantation for these kinds of salvage procedures (Kaufman et al.., 2013; Siemionow, Gharb, & Rampazzo, 2013; Weissenbacher et al., 2013). We report the first case in the literature of the removal of an allotransplanted face and its replacement with a free flap due to an unfavorable, complex situation. Difficulties and rescue procedures in face allotransplantations are discussed based on this challenging case.

2 | CASE REPORT

The recipient was a 54-year-old man with disfigurement of the entire face following an accidental gunshot injury 5 years previously. Five

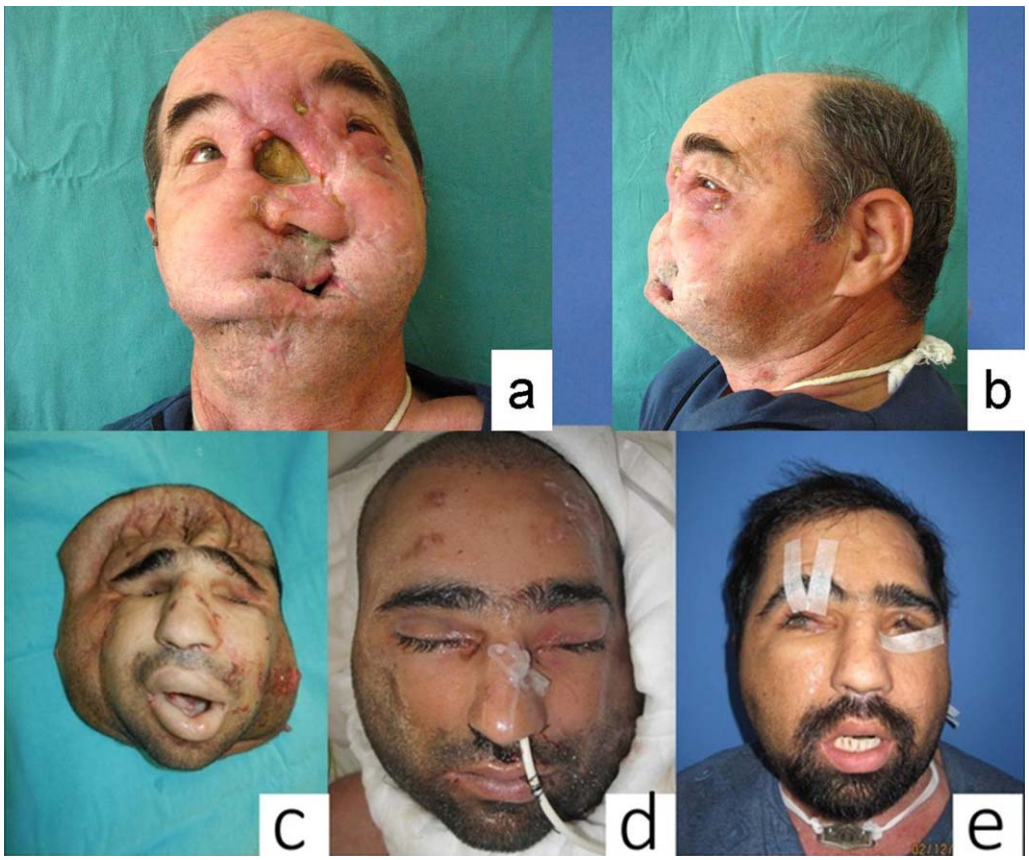

FIGURE 1 Patient appearance immediately before facial allotransplantation, a: frontal view, b: right profile, c: intraoperative photographs of the donor allograft specimen, d: immediate postoperative photographs, e: patient appearance 3 months after facial allotransplantation

sequential surgical procedures had been performed previously in another center. The large defect included the maxilla, mandible, and mid-face (Figure 1a,b) Feeding before transplantation was via gastrostomy, and breathing was via tracheostomy. The patient could not speak intelligibly. Drooling was present, together with social disintegration and isolation due to malodor. The patient had no sense of smell, and was unable to make any meaningful mimic movements. Cytomegalovirus (CMV) Ig M was negative, and CMV Ig G was positive. Similarly, Epstein-Barr virus (EBV) IG M was negative, and EBV Ig G was positive. Panel reactive antibody (PRA) screening was negative. Both complement-dependent cytotoxic crossmatch (CDC) and flow cytometric crossmatch (FCXM) were negative.

The donor was a 35-year-old man whose blood group was compatible with five HLA-A, -B, and -DR mismatches, as well as negative lymphocyte cross-matches. Both CMV and EBV Ig serologies were similar to those of the recipient (negative IgM and positive Ig G). Full face procurement was performed, including all facial skin and facial musculature, both eyelids, the nasal bone, the maxilla, part of the mandible, the base of the tongue and the anterior part of the scalp (Figure 1c). Arterial anastomoses were performed between external carotid artery matches in an end-to-end manner. Venous anastomoses were performed between the external jugular veins in an end-to-end manner and the internal jugular veins in an end-to-side manner, bilaterally. The recipient was transferred to the intensive care unit, where he was monitored for 2 days. He was transferred to the floor once his vital signs had been stabilized.

Antithymocyte globulin (ATG) and prednisolone were administered in the initial induction period. Maintenance treatment consisted of prednisolone (20 mg/day), tacrolimus (blood levels between 15 and 20 ng/mL) and mycophenolate mofetil (MMF) (2 g/day).

Broad spectrum antibiotic therapy was administered for the first 10 days postoperatively in order to prevent infectious complications. Sulfadoxine pyrimethamine was administered in order to prevent *Pneumocystiscarinii* pneumonia. Oral nystatin drops were administered for fungal prophylaxis, and oral valacyclovir tablets for CMV prophylaxis.

There were no complications due to surgery, and no rejection was determined in the early postoperative period (Figure 1d,e). The patient started to eat and drink smoothly. Five months postoperatively, two small ulcerative lesions appeared on the dorsum of the left hand and the right pretibial regions (Figure 2a,b). Biopsy specimens identified both lesions as squamous cell carcinoma, and large excisions covered with split thickness skin graft were performed (Figure 2c,d). One month later (6 months postoperatively), the patient presented with a rapidly growing 2 × 2 cm ulcerative nodule (lymph node) in the left preauricular region. Total excision of the mass was performed, and histopathological examination revealed a CD-20 positive diffuse large B cell lymphoma (Figure 3a,b). Positron emission tomography/computed tomography (PET/CT) scan and bone marrow biopsy were performed

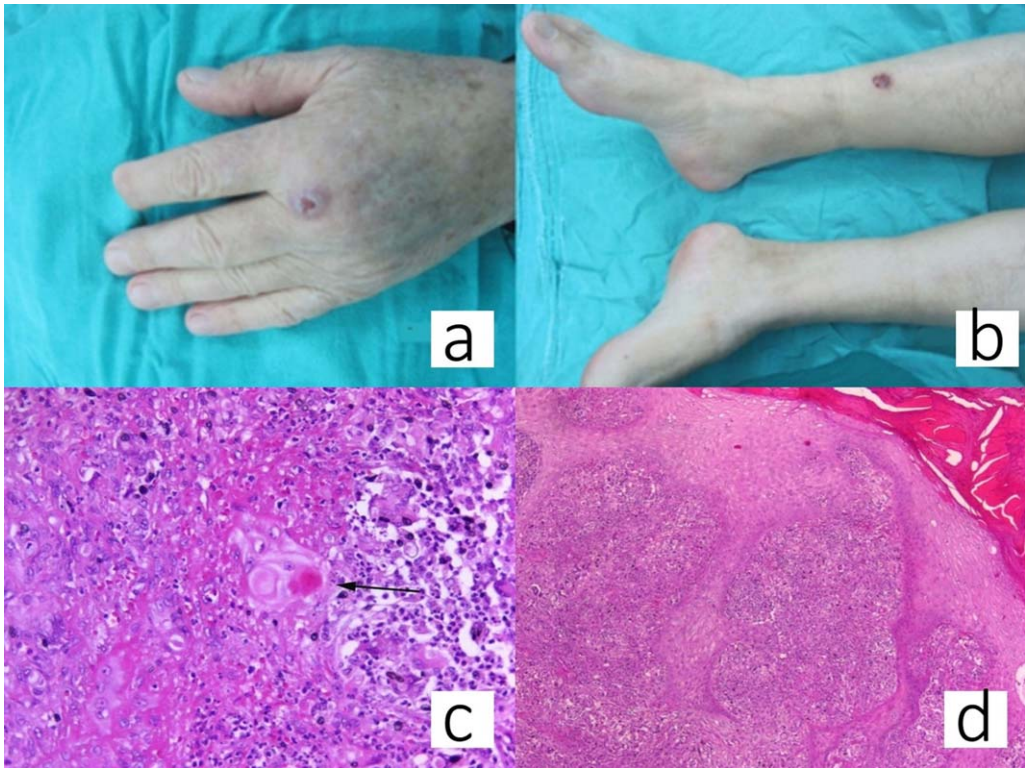

FIGURE 2 Squamous cell carcinoma, a: of the upper leg, b: lower leg, c: dermal invasion with squamous cell carcinoma (HE ×200), d: moderately well-differentiated squamous cell carcinoma (HE ×40)

in order to stage the lymphoma. Intense fluorodeoxyglucose (FDG) uptake was detected only in the unilateral inguinal lymph node. Excisional biopsy was performed, and this lymph node was again diagnosed as CD-20 positive diffuse large B cell lymphoma. Chimerism analysis using the short tandem repeat method revealed fully autologous signals of recipient origin. The patient was diagnosed with Stage IIIA non-Hodgkin lymphoma (NHL), and treatment was started with reduction of immunosuppressive treatment and R-CHOP regimen (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone). A low level of tacrolimus was administered, maintaining a blood level of 2-3 ng/ml, with 5 mg of prednisolone. Although rapamycin had been started in order to reduce the tacrolimus dosage and to benefit from its antitumor effect, this was stopped one week later because of pulmonary complications such as dyspnea on exertion and dry cough.

Extensive cough developed during the second cycle of treatment. Thoracic computed tomography (CT) was performed and showed cavitation. Galactomannan antigen was determined as positive in blood and bronchoalveolar lavage samples. Based on these findings, aspergillosis was diagnosed, and liposomal B was started, the dose being adjusted based on increasing creatinine levels. Wide spectrum antibacterial antibiotics were administered together with antifungal treatment. Control PET/CT scanning revealed a highly active area in the right cerebellum. Magnetic resonance imaging (MRI) was performed for confirmation of diagnosis, and a 1-mm lesion was identified close to the pons (Figure 3c). Following consultation with the neurology and brain surgery departments, it proved impossible to take a biopsy sample from the lesion because of its location. The lesion was thought to represent cerebellar aspergillosis. However, this could not be differentiated from central nervous system lymphoma. The patient developed ataxia during walking, concordant with the cerebellar lesion. The immunosuppressive agents were stopped completely. The risk of rejection was monitored with serial biopsies taken from the skin and oral mucosa and clinical observation.

On the 281st day of hospitalization, hypotension and loss of consciousness occurred, accompanied by a decrease in arterial O_2 saturation. The patient underwent elective intubation and was placed on a mechanical ventilator. Urine output decreased progressively, and bilateral fine rales were observed. Continuous venovenous hemofiltration dialysis was started. On the 3rd day of mechanical ventilation, paroxysmal atrial fibrillation (PAF) attacks started, compromising arterial blood pressure. During these observations, marked skin atrophy and hyperpigmentation developed in the face allograft. Biopsy specimens revealed grade 2 rejection (Figure 4a-c). On the 16th day of mechanical ventilation, vital findings were as stable as possible. In order to prevent further rejection and adverse affects and minimize the metabolic and immunological load of the transplanted tissue on the body, surgery was performed to remove the transplanted tissue and replace it with a free flap. Two teams worked simultaneously. The pedicles of the flap, the external carotid arteries and internal jugular veins were located. The anastomoses were ligated bilaterally. All skin, subcutaneous layers, muscle, parotid glands and mucosa were removed, as well as the bony segments of the maxilla, mandible, nose, and zygomatic arch. All surrounding soft tissues and teeth segments were removed on the table. These were then replaced in their original locations as bony allografts.

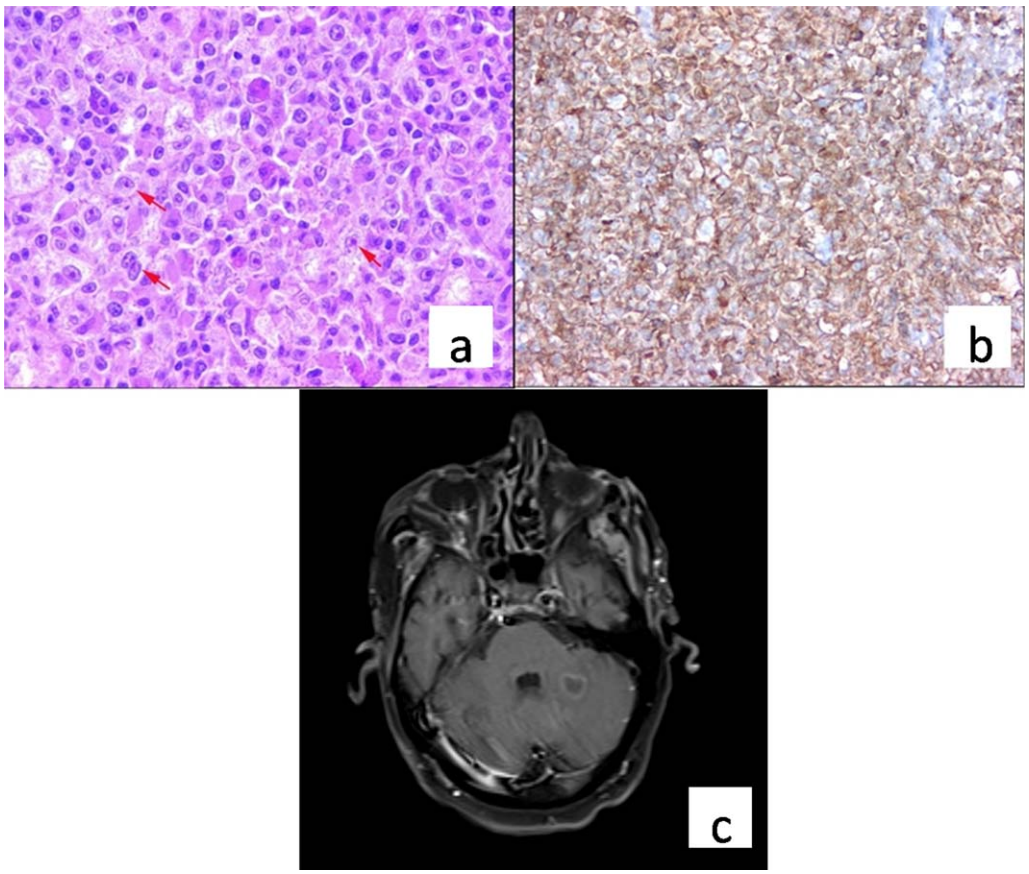

FIGURE 3 a: Diffuse infiltration by a large atypical lymphoid cell population(HE ×400), b: these atypical cells were immunopositive for CD20 (CD20 × 200), c: T1-weighted postcontrast transverse image shows peripherally enhancing lesion within left cerebellar hemisphere

(Figure 4d-f) Soft tissue coverage was performed with a large free anterolateral thigh (ALT) flap (16 × 30 cm). The flap was harvested on four separate perforators based on one main vascular pedicle. Incisions were made among these perforators in order to recreate the orifices of the eyes, nose, and mouth (Figure 4 g,h). The anastomoses were performed to the external carotid artery in an end-to-end manner, and to the internal jugular vein in an end-to-side manner. The entire procedure lasted 5 h. The patient was transferred to the intensive care unit postsurgically. Postoperative recovery was uneventful, and all vital signs appeared to be improving in the early hours postoperatively. Blood sample tests were within normal ranges. On the 4th week of intubation, partial O_2 pressure decreased suddenly despite optimal mechanical ventilator settings. The patient died despite a prolonged attempt at cardiopulmonary resuscitation at the end of post-transplantation month 11. Autopsy was recommended for differentiation between aspergillosis and lymphoma, but permission was refused by the family. Biopsy examination of the removed transplanted tissue revealed grade 1 to 2 rejection.

3 | DISCUSSION

Lifetime use of immunosuppressive drugs is the major risk involved in nonlife saving procedures, including face and extremity transplantations, as in all other solid organ allotransplantations. Although their long-term results have not yet been fully determined, there are a number of immunomodulation therapies available for minimizing complications, including administration of steroid free protocols and cell-based protocols such as the use of mesenchymal stem cells (Leonard, Cetrulo, McGrouther, & Sachs, 2013; Leonard, Kurtz, & Cetrulo, 2014; Ravindra, Xu, Bozulic, Song, & Ildstad, 2012). Although experimental studies have been performed, clinical trials reporting interim results and controlled multicenter trials are now needed in order for progress to be made in this field and for acceptance to be obtained. Many factors attendant upon long-term use are still unknown, including effectiveness, advantages, disadvantages and side-effects. Importantly, none of the protocols described to date has been proved to be effective in all cases. Additionally, with a few exceptions, the majority of centers still rely on conventional immunosuppressive regimens. We have used the same conventional triple immunosuppressive regimen in all other face and composite tissue transplantation cases in our solid organ transplantation center.

Roche, Blondeel, Van Lierde, and Vermeersch (2015) reported a recent update and history of face transplantation. They reported that overall functional outcomes are good and satisfaction levels are high, surpassing initial expectations. The main complications described were opportunistic infections, with four deaths occurring (five together with the present case and the recent patient from Amiens).

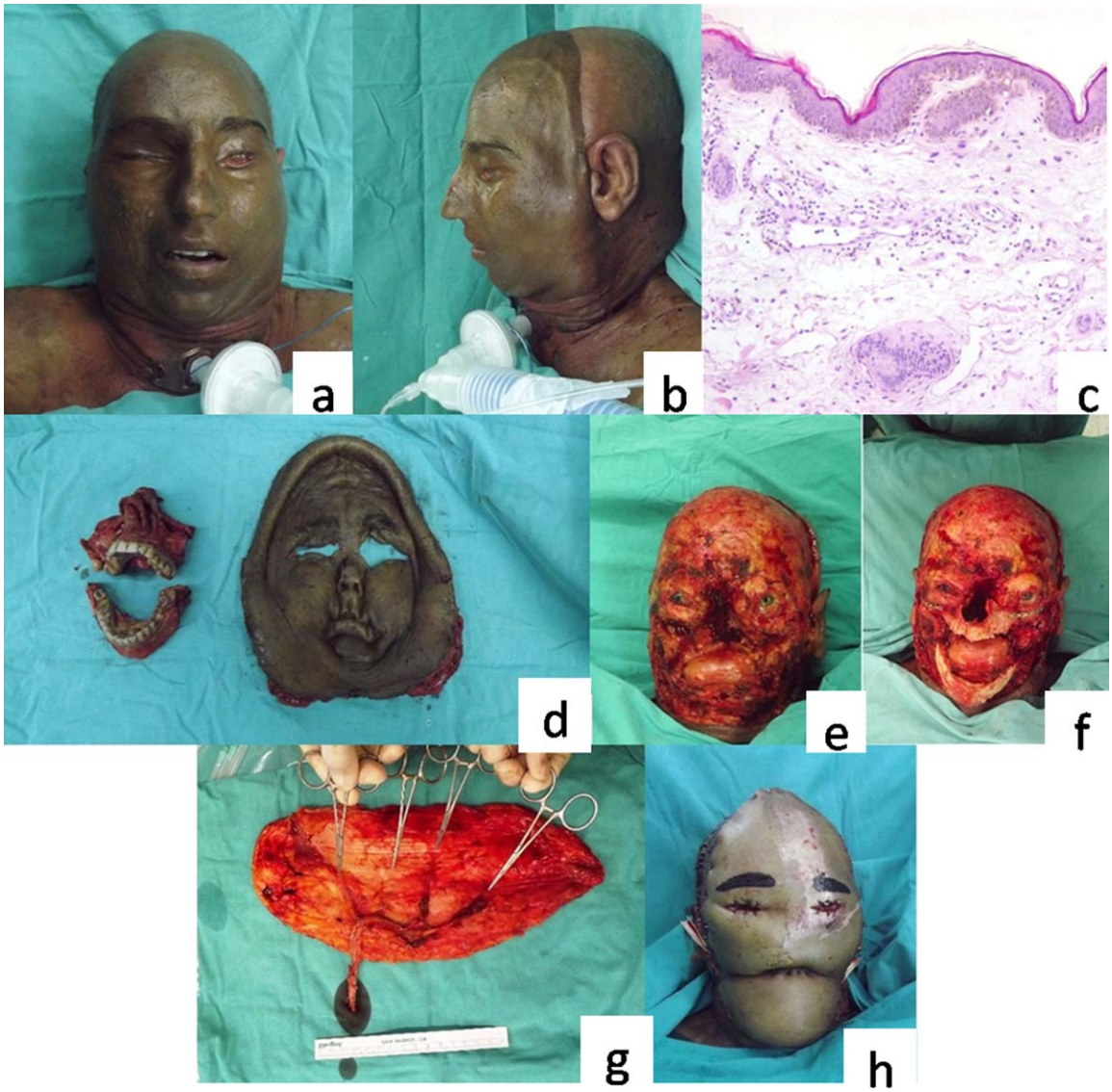

FIGURE 4 Image before transplanted tissue removal. Note the skin atrophy and hyperpigmentation of the face. a: Frontal view, b: left profile, c: mild perivascular dermal immune cell infiltration(HE ×100), d: removed allografts specimens, e: intraoperative photograph of patient face after the allograft specimen was removed, f: the bones were then replaced in their original location as bony allografts, g: intraoperative view of the harvested ALT flap, the flap was harvested on four separate perforators based on one main vascular pedicle, h: immediate postoperative view, note the amateur make-up for eyebrow reconstruction

Malignancy is one possible catastrophic complication observed in transplanted patients. Although sufficient data are lacking for vascularized composite allotransplantation (VCA) cases, nonmelanoma skin cancers (NMSC) are the most common de novo malignancies seen in solid organ transplanted patients. Of these, squamous cell carcinoma is the dominant type and exhibits more aggressive behavior, with a high incidence of local recurrence and metastasis and high mortality (Piselli et al., 2014; Singavi, Harrington, & Fenske, 2015). To date, four VCA recipients (two hands and two faces) have developed post-transplant NMSC (BCC, SCC and premalignant lesions). Tumors have been treated by surgical excision and premalignant lesions using cryotherapy (Kanitakis et al., 2015).

It is of the utmost importance to consider the high risk of previously treated tumor recurrence in allotransplantation procedures. In 2009, an HIV positive patient undergoing face transplantation in Valencia, Spain suffered a resection of squamous cell carcinoma of the head and neck 11 years previously. The patient died due to recurrence of tumor (Diaz-Siso, Sosin, Plana, & Rodriguez, 2016).

Post-transplant lymphoproliferative disorders (PTLD) are the second most common malignancies in transplanted patients. These exhibit different histopathological findings compared with lymphoproliferative malignancies seen in the general population, with characteristically more aggressive behavior. They are less responsive to conventional treatment, and outcomes are generally poor. PTLD comprise a wide spectrum of disorders ranging from benign hyperplasia to aggressive non-Hodgkin's lymphoma (NHL). PTLD occurring within 12 months postoperatively is described as early PTLD. It has been suggested that these disorders may be related to EBV (Kinch et al., 2014). The present

case was already EBV-positive (IgG positive, IgM negative) preoperatively and met proper match criteria with the donor. IgM was still negative postoperatively. Reducing or withdrawing immunosuppression is the first step in treatment and is of great potential benefit in prognosis. The second face transplant from Amiens, France, developed an EBV-related B-cell lymphoma 14 months after transplantation and was treated with rituximab (Diaz-Siso et al., 2016; Kanitakis et al., 2016; Kinch et al., 2014). Recurrence requiring chemotherapy with cessation of immunosuppression subsequently developed. Following complete remission, the patient was diagnosed with an EBV-related smooth muscle cell tumor of the liver 3 months subsequently. Starting from the second post-transplant year, the transplanted facial skin became progressively sclerotic and presented pigmented macules against a background of hypopigmentation and teleangiectasias. Although there was no formal definition of chronic rejection in human VCA, skin biopsies strongly suggested evidence of chronic rejection, the first such report in the literature in a case of face transplantation following minimization of immunosuppression (Kanitakis et al.., 2016; Petruzzo et al., 2015). Chronic rejection in most cases clearly resulted from a decrease or discontinuation of the immunosuppressive regimen, either due to patient noncompliance or from a need to reduce the dosage due to complications associated with the immunosuppressive treatment.

Although skin cancer and PTLD are the major concerns for *de novo* malignancy, higher levels of all types of malignancy can be seen compared with the nontransplanted population. The first face transplant recipient developed cervical carcinoma *in situ* 50 months post-transplant (Petruzzo et al., 2012). This was treated with cone excision. In 2010, bilateral pneumopathy occurred and was successfully treated with antibiotics. Unfortunately the patient's death from lung cancer was reported by the media in September 2016. Death actually took place on April 22, 2016, although the announcement was delayed in order to respect the family's privacy.

The high risk of life-threatening fungal infection is still a major challenge in allotransplanted patients. Aspergillus is the second most common fungal infection, after Candida, and one that can involve nearly all organs. Early detection is almost impossible due to nonspecific clinical manifestations. It is usually diagnosed when it is already well disseminated, and mortality rates can be as high as 100%. Although the probability of success is low, if life is to be saved, early detection is crucial for the administration of effective antifungal treatment and, if possible, for the removal of infected original lesions. Accurate microbiological diagnosis may not always be possible, and treatment may proceed based on clinical findings, radiological imaging and indirect blood test results, such as positive antigen levels. Central nervous system involvement represents a specific cause for concern, with a low probability of response to therapeutic modalities and very high mortality rates (Barchiesi et al., 2015; Hoyo et al., 2014; Meng et al., 2014). Adjustment of immunosuppressive drugs, lowering the doses employed or even stopping them entirely, may be life-saving. Unidentified clinical signs or pathological findings in system investigations, such as the pulmonary or central nervous system or renal involvement, should also be kept in mind.

The three major complications, including skin malignancy, PTLD and aspergillosis, in our case may be attributed to the level of immunosuppressive regimen employed. One of the most challenging problems is to establish a balance between preventing acute rejection and simultaneously avoiding potentially life-threatening complications (Bonastre, landin, Diez, Casado-Sanches, & Casado-Perez, 2012). This requires a careful balance in the selection and dosage of immunosuppressive regimens. Rodriguez's team performed a similar transplantation of total face, double jaw and tongue following a close-range, ballistic facial injury sustained in 2012 (Diaz-Siso et al., 2016). The patient had experienced three episodes of acute rejection in the first 4 years post-transplant. The currently generally used conventional regimens and doses are quite similar in most major centers. We have used a similar protocol with no significant problems in all our other vascularized composite tissue transplantation cases and in all solid organ transplantations. The most logical hypothesis may be a predisposition and high sensitivity on the part of the patient to immunosuppressive complications that could not be envisaged preoperatively.

Surgical rescue procedures in vascularized composite tissue transplantations in the event of unexpected situations are exceedingly challenging. Most patients will have already exhausted all conventional reconstructive options before face transplantation is added to the list. Salvage procedures may be required in several situations, including surgical complications (failures due to technical or early immunological and ischemic causes), psychological noncompliance on the part of the patient, the need to withdraw immunosuppressive drugs due to opportunistic infections, heavy metabolic complications and malignancies, and chronic rejection. In the case of failures resulting from technical causes, requiring a patient who has already received an urgent face transplantation to undergo another transplantation procedure seems to be the only acceptable solution. However, the patient should be reconstructed using conventional methods, at least in the early period. In all other situations, facial re-transplantation should not be regarded as an option. All possible efforts should be made to reconstruct the patient using conventional methods. Although in the case of partial face transplantation the reconstructive procedure and results may be acceptable compared with the preoperative appearance, even when total face transplantation is performed using all reconstructive tools the outcome may still not be comparable with the preoperative appearance (salvage procedure will be absolutely more difficult and less acceptable in total face transplantation than in a partial one). Removal of the face allograft and replacement with a free flap may represent the best rescue procedure for saving the patient's life. In order to reduce operative time, simplify the procedure and reduce donor side morbidity, we used nonvascularized bone grafts prepared from a resected allograft and a simple fasciocutaneous free flap with a reliable and safe vascular pedicle. Although the immediate postoperative appearance was far from ideal in cosmetic terms, it would not be difficult to revise the transferred tissues using reconstructive tools including autologous tissue revisions and use of prosthetic epitheses.

The challenge involves not only the choice of reconstructive method, but also the medical status of the patient in a life-threatening

condition. As in our case, it may not be possible to achieve an ideal stable situation, and the procedure may have to be performed under highly risky conditions. Although at the time of surgery our patient had only grade 1 rejection (this might be graded as 2 near to the last stage, but certainly no more than grade 2, as shown in Figure 4c), skin atrophy and pigmentation were present. We had no doubt that the transplanted tissue would be rejected without immunosuppression. That would in turn necessitate emergency surgery at an unexpected time without proper preparation due to adverse effects and the metabolic and immunological load of the transplanted tissue on the body due to massive rejection. We waited for the optimal time for surgery, even at the beginning of the early period of rejection, in order to prevent further situations that might be impossible to control. The benefit to risk ratio should be discussed in detail, and the responsibility must be shared between all the relevant specialties. Monitoring a patient without immunosuppressive treatment while simultaneously recording a low degree of rejection may be thought of as an interesting approach. However, considering our patient's general poor health status and also heavy neutropenic conditions resulting from the chemotherapy regimen, we did not encounter a heavy rejection attack at least until the patient's death.

This case represents the first attempt in the literature at a rescue procedure after face transplantation. Although the early postoperative rescue period was promising, the metabolic load from the previous period probably obviated success, and the procedure failed to save the patient. In speculative terms, we suggest that the patient's immunological load should be reduced as soon as stable medical conditions are achieved in case of diagnosis of malignancy and untreatable opportunistic infections, including withdrawal of all immunosuppressive drugs and removal of all allotransplanted tissues. In terms of self-criticism, had we performed the rescue procedure in the early period of diagnosis of skin cancer and PTLD, the probability of success would have been higher, at least in terms of better patient status without opportunistic infection. We believe that this method for rescue surgery represents a good alternative for similar situations in the future in the context of a better status and earlier diagnosis than in this case.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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