Management of Steroid-resistant Late Acute Cellular Rejection Following Face Transplantation: A Case Report

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ABSTRACT

Face transplants have been clinically established, and early acute rejections have been reported. Late acute rejections have been less common. Immediate and accurate diagnosis along with successful treatment is critical to prevent graft damage. This case report describes the successful treatment of a severe, steroid-resistant rejection 2 years after a full face transplant.

THE FIRST human face transplant was performed in 2005 [1]. As of 2012, there have been 2 partial and 3 full face transplants in the United States [2]. Although face transplantation is still considered experimental, benefits of a partial or full face transplant have been broadly recognized. Aside from obvious physical deformities, injuries to the face may cause significant limitations of speech and swallowing in addition to psychological and social dysfunction [1].

Rejection of vascularized composite tissue transplants is common, and early and accurate diagnosis is important to prevent irreversible graft damage and loss [3]. Visual inspection together with histopathologic evaluation of the skin is the gold standard in the diagnosis of rejection in vascularized composite allotransplants (VCAs) [4]. Histopathological criteria have been standardized and graded at the Ninth Banff Conference on Allograft Pathology in 2007 [5]. Reports on late and severe acute rejections and their diagnosis, treatment, and outcome remain limited. The purpose of this article is to describe a case of successful treatment of severe rejection in a full face transplant recipient in the United States.

CASE REPORT

We report on a 27-year-old Caucasian man who underwent a full face transplant in 2011 at Brigham and Women's Hospital in Boston, Mass. He had suffered from fourth-degree electrical burns in 2008, causing severe soft tissue and bony injury and leaving him blind. The patient underwent subsequent reconstruction using 4 free muscle flaps and bilaminate neodermal reconstruction. Following face transplantation, he was weaned off steroids and remained on stable, dual therapy with tacrolimus and mycophenolate for 2 years. Of note, he had a panel reactive antibody (PRA) of <70. His cross-match had been negative (for both complement-dependent cytotoxicity and flow), and he did not have donor specific antibodies. His tacrolimus levels had been consistently in a range of 3–6 ng/mL after his first year post-transplantation. Protocol biopsy results had been normal, and he had no clinical signs of rejection.

Two years after his transplant, he presented with complaints of flu-like symptoms including low-grade fevers, fatigue and malaise, diffuse body aches, sore throat, and cough for the past 5 days. The patient reported nasal congestion, sneezing, and sinus and facial pressure. He complained of his face "feeling tighter" but denied any outward pain to his face. His sentinel flap, skin from the donor's forearm placed near the groin as an indicator of rejection and to spare the face from multiple biopsies, presented with subtle diffuse, patchy erythema, primarily at the margins [6]. The patient reported that he was recently exposed to a young child diagnosed with an ear infection while at an indoor water park. Physical presentation revealed full facial erythema and edema. Vital signs were stable and he was afebrile. A computed tomography scan of his head and neck revealed no acute abnormalities, including absence of sinusitis, and

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his chest radiograph was unremarkable. A punch biopsy sample was taken from both the face and sentinel flap. The patient was admitted and received methylprednisolone 500 mg intravenously based on the clinical presentation of an acute rejection.

The patient received empiric intravenous vancomycin and piperacillin/tazobactam to treat cellulitis in addition to micafungin for fungal coverage until final results from cultures were available. For his flu-like and upper respiratory symptoms, the patient received a course of oseltamivir and levofloxacin. The patient received sulfamethoxazole/trimethoprim for pneumocystis prophylaxis and valganciclovir for cytomegalovirus (CMV) prophylaxis while receiving treatment for rejection.

His infectious workup was negative for human immunodeficiency virus, fungal and bacterial blood cultures, sputum culture for acid-fast bacillus, fungus, and *Nocardia*; his urine culture was negative; moreover, Epstein-Barr virus and CMV were negative by polymerase chain reaction, and his nasal wash, respiratory viral antigen and culture, rapid strep antigen, *Legionella* antigen, *Mycoplasma* serology, and *Chlamydia* serology were all negative.

His tacrolimus level at presentation was 2.8 ng/mL, and the dose was adjusted to maintain levels of 10–12 ng/mL. Routinely processed hematoxylin and eosin–stained biopsy samples of facial skin and sentinel flap from admission showed mild to moderate perivascular inflammation with focal dyskeratotic and apoptotic keratinocytes in the epidermis and follicular epithelium, compatible with grade II–III Banff 2007 rejection. Tacrolimus 0.1% topical ointment was applied twice a day to his face, in addition to fluocinonide 0.05% topical cream. His mycophenolate dosage was increased from 1000 to 2000 mg/day. With only minimal improvement, methylprednisolone 250 mg intravenously was given daily for 3 additional days.

The patient began developing ulcerations on his lip mucosa, and a subsequent biopsy samples of his face and sentinel flap were obtained 10 days after the biopsy at admission (Fig 1 and Fig 2). The second biopsy showed mild perivascular inflammation with focal epidermal dyskeratosis/apoptosis compatible with grade III Banff 2007 rejection. The patient received 3 doses of 1.5 mg/kg antithymocyte globulin (rabbit ATG, Thymoglobulin, Genzyme, Cambridge, Mass., United States), and an additional biopsy sample of the lip mucosal lesion was negative for any viral infections but was still showing individually necrotic keratinocytes compatible with grade III Banff 2007 rejection.

Fig 1. Lips (mucosa): Banff 2007 grade III rejection.

Fig 2. Banff 2007 grade III rejection.

Treatment was then continued with an additional 2 doses of 1.5 mg/kg anti-thymocyte globulin for a total of 5 doses. Dexamethasone mouth rinses and tacrolimus 0.1% ointment were applied to upper and lower lips and buccal mucosa 3 times a day. One week later, the lip ulcerations were nearly healed. A third biopsy sample of his face and sentinel flap was obtained 8 days after the prior biopsy, showing progressive resolution consistent with Banff 2007 grade II rejection.

Two months after initial presentation, the biopsy samples of both the face and sentinel flap showed resolution of the rejection and only sparse infiltrate with minimal change. More than 10 months after the acute rejection, the patient is currently on a dual immunosuppression regimen with tacrolimus and mycophenolate. Tacrolimus trough levels have been maintained at 5–7 ng/mL.

DISCUSSION

Early rejection is frequent in VCA recipients. Late acute rejection usually occurs after reductions of immunosuppression or after viral infections [7]. Skin is usually the first target to manifest changes suggestive of acute rejections in VCA with edema and visible erythema [8]. Histological examination usually confirms the diagnosis but changes may not be specific for acute rejection, and other inflammatory and infectious complications need to be considered in the differential diagnosis [7].

In our patient, the face and sentinel flap biopsy samples were confirmatory of rejection; however, the sentinel flap did not present clinically as severely as the face. The sentinel flap has been reported to be a reliable marker of rejection, and visual rejection usually appears earlier in the sentinel skin graft than in the face [6]. Reported rejections usually respond to steroid bolus doses and increase in maintenance immunosuppression [9,10]. Polyclonal or monoclonal antibodies have been used in some cases of severe acute rejection of VCA [7].

Our case demonstrates the first successful treatment of steroid-resistant late rejection following face transplantation. This case demonstrates that late acute rejections can be successfully treated and that maintenance immunosuppression can be scaled back to a low-dose dual treatment. Avoiding low

tacrolimus levels (<4 ng/mL) seems critical for the prevention of late acute rejections.

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