A case of facial composite tissue allograft rejection

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INTRODUCTION

Facial composite tissue allotransplantation is an emerging treatment for patients with severe facial defects. Despite its promise, rejection remains a significant challenge because of the high immunogenicity of donor skin. In fact, acute rejection affects nearly all facial composite tissue allotransplantation recipients within the first postoperative year.[1] The novelty of facial composite tissue allotransplantation has limited our understanding of the rejection process.

CASE REPORT

A 27-year-old man underwent facial composite tissue allotransplantation after sustaining severe facial deformities after a self-inflicted gunshot wound. The HLA antigen mismatch was 1-1-2 for A, B, and DR (donor A2, 68; B35, 44; C4, 16; DR4, 7, 53; and DQ2, 8; and recipient A32, 68; B44; C5, 7; DR9, 15, 51, 53; and DQ6, 9). He received initial induction (antithymocyte globulin, solumedrol, and rituximab) and maintenance immunosuppression (tacrolimus, mycophenolate mofetil, and prednisone).

Eighteen months after his facial composite tissue allotransplantation, the patient presented to the emergency department after several weeks of persistent allograft erythema involving the central aspect of the face and neck without associated swelling (Fig 1). He was admitted because of concern for acute rejection and found to have donor-specific antibodies to C4. A skin biopsy of the allograft on the day of presentation revealed a patchy, bandlike, predominantly lymphocytic infiltrate with admixed eosinophils and plasma cells. The epidermis was irregularly hyperplastic with hypergranulosis and interface changes involving the tips of the rete ridges primarily. Slightly thickened collagen bundles were also noted (Fig 2). The infiltrate was composed of $CD3^+$ T cells with a slight predominance of $CD4^+$ T cells in comparison with $CD8^+$ T cells. In light of the clinical features, these findings were concerning for rejection.

The patient received pulse steroids, with noticeable improvement of his facial erythema and reduction in donor-specific antibodies. A repeated biopsy after the first day of methylprednisolone revealed a significant reduction in the density of the lymphocytic infiltrate. Interface changes were present but diminished. The inflammatory infiltrate was composed almost entirely of $CD3^+$ T cells with a CD4 to CD8 ratio of 2:1. The patient was discharged with a prednisone taper. Two months after his initial episode, he returned with recurrent facial erythema and new hyperpigmentation (Fig 3). Repeated allograft biopsy revealed fibrosis and sclerosis with dilatated thin-walled blood vessels and loss of adnexal structures (Fig 4). The patient again received pulse steroids, with clinical improvement.

DISCUSSION

Facial composite tissue allotransplantation and other vascularized composite allografts differ significantly from traditional solid organ transplant because of the presence of skin, which is rich in donor-antigen-presenting cells and resident T cells.[2] The skin is therefore highly immunogenic and serves as the primary target in acute facial composite tissue allotransplantation rejection.[1]

Several distinct pathways of allorecognition and T-cell activation have been described in accordance with data from animal models and solid organ

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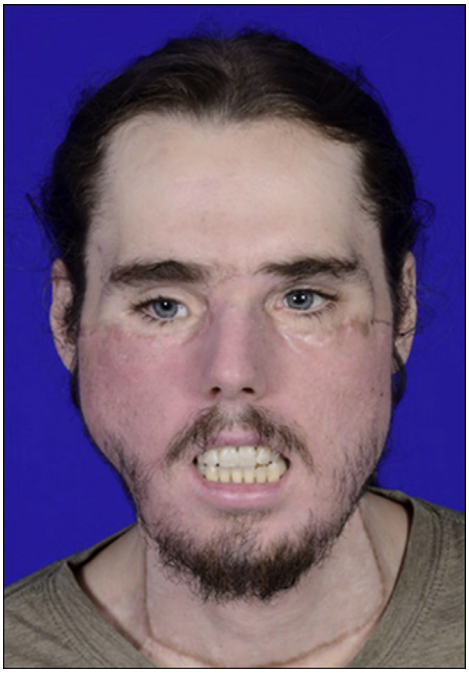

Fig 1. Patient's head and neck on initial presentation, showing faint erythema of the mid and lower aspect of the face and anterior aspect of the neck at initial presentation. The biopsy (see Fig 2) was taken from allograft skin on the right side of the patient's neck, adjacent to the suture line. (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS.)

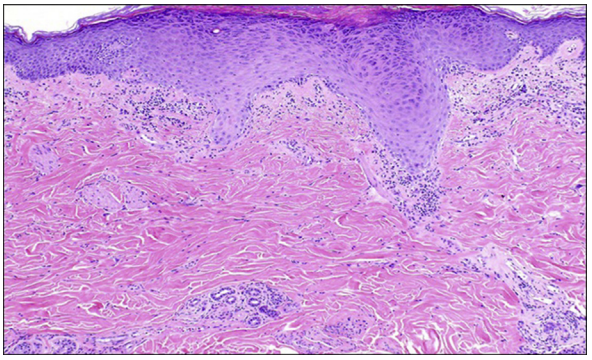

Fig 2. Histologic findings of the biopsy taken from the right side of the neck on the day of admission during the patient's first episode of rejection, showing a patchy lichenoid infiltrate with epidermal hyperplasia and hypergranulosis. (Hematoxylin-eosin stain; original magnification: ×200.) (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS.)

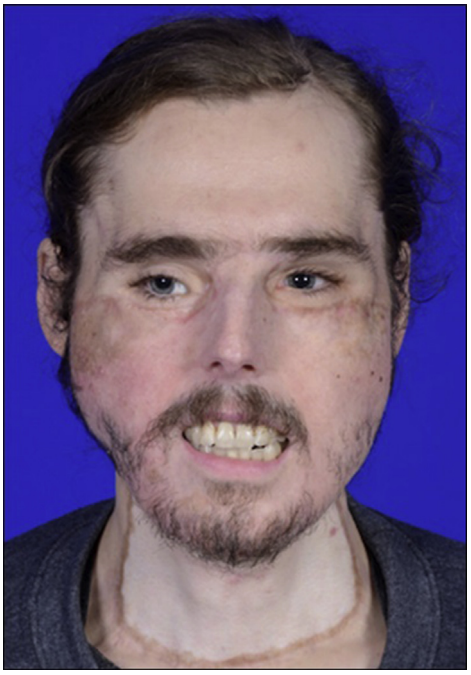

Fig 3. Patient's head and neck 2 months after his initial presentation, during which he presented with recurrent facial erythema. Patchy erythema and hyperpigmentation can be seen in the mid and lower aspects of the face. A confluent patch of hypopigmentation is visible in the neck allograft. The biopsy (see Fig 4) was taken from allograft skin on the right side of the patient's neck, adjacent to the suture line. (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS.)

transplant.[2] The direct pathway, which is thought to be involved in early alloimmunization, involves the presentation of intact antigen by donor-antigen-presenting cells to recipient T cells.[3,4] In the indirect pathway, recipient-antigen-presenting cells process and present major or minor histocompatibility peptide complexes to recipient T cells.[3,4] The indirect pathway serves as a mechanism for immunoactivation that persists for the duration of the graft.

The histologic changes in acute vascularized composite allograft rejection are graded according to the 2007 Banff working classification. Mild acute rejection exhibits a perivascular inflammatory pattern,[5] whereas more severe cases exhibit a higher-density inflammatory infiltrate and may be accompanied by interface and adnexal changes.[5,6] Although the Banff system provides a helpful approach for evaluating acute rejection, there are now reports of new histologic patterns not encompassed in the 2007 criteria.

For example, the dermal sclerosis and lichenoid changes observed during our patient's initial presentation are not included in the Banff system, but similar findings have been described in a facial composite tissue allotransplantation patient by Petruzzo and colleagues.[7] Their patient had a similar clinical course, with repeated episodes of facial edema and erythema that were associated with histologic findings of a lichenoid infiltrate, and later

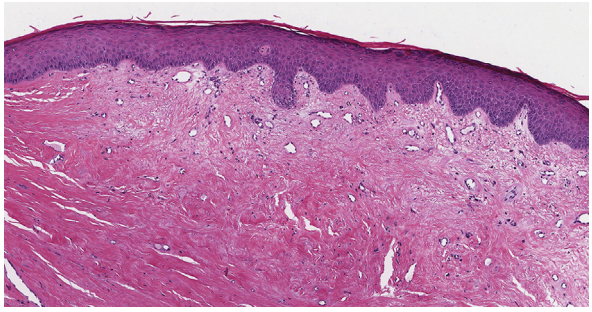

Fig 4. Repeated allograft biopsy 2 months after the patient's initial presentation, showing fibrosis and sclerosis with focal follicular interface changes. (Hematoxylin-eosin stain; original magnification: ×100.) (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS.)

developed cutaneous discoloration and clinically sclerotic-appearing skin in the setting of reduced immunosuppression.[7] Repeated biopsies showed diffuse dermal sclerosis, which encased the dermal capillaries, and sweat gland atrophy.[7] Kanitakis et al[8] also reported a case of hand allograft rejection that presented with recurrent episodes of hyperkeratotic lichenoid papules and histologically had capillary thrombosis in the upper dermis, with a dense perivascular infiltrate. Because all 3 patients had recurrent episodes of rejection, lichenoid inflammation may be a hallmark of repeated acute rejection, persistent or subclinical acute rejection, or inadequate immunosuppression. Indeed, our patient had several weeks of facial erythema before initial presentation and inconsistent follow-up between the 2 episodes of rejection.

Recurrent or incompletely treated acute rejection may allow the priming of T cells in the skin, resulting in the development of lichenoid inflammation. A similar mechanism has been proposed for fixed lichenoid drug reactions, which are thought to be mediated by $CD8^+$ T cells primed by viral infection and later persist in the skin as resident effector memory T cells. Most of the lymphoid infiltrate in the epidermis of vascularized composite allograft skin is composed of $CD8^+$ donor-derived T cells, which express resident memory T-cell markers.[2] However, in our patient and in the case described by Petruzzo et al,[7] skin biopsies showed an inflammatory infiltrate composed predominantly of $CD4^+$ T cells.

Sclerotic changes may represent chronic allograft damage. Dermal sclerosis has been demonstrated in monkey models of chronic rejection,[8,9] and Petruzzo et al[7] have suggested that it may evince chronic rejection in humans as well. The 2013 Banff meeting recognized loss of adnexal structures and dermal sclerosis as potential signs of chronic rejection.[10] Therefore, lichenoid inflammation may portend the development of sclerosis and chronic rejection or represent an early or milder form of chronic rejection. Alternatively, it has been proposed that dermal sclerosis and lichenoid inflammation represent a form of graft-versus-host disease-like reaction in the skin.[7]

CONCLUSION

As the collective experience with vascularized composite allograft increases, the greater range of clinical, histologic, and perhaps also chronic changes will allow continued revision of diagnostic criteria and a better understanding of the immunologic mechanisms of vascularized composite allograft rejection.

REFERENCES

1. Morelon E, Petruzzo P, Kanitakis J. Chronic rejection in vascularized composite allotransplantation. *Curr Opin Organ Transplant*. 2018;23:582-591.
2. Fischer S, Lian CG, Kueckelhaus M, et al. Acute rejection in vascularized composite allotransplantation. *Curr Opin Organ Transplant*. 2014;19:531-544.
3. Sarhane KA, Khalifian S, Ibrahim Z, et al. Diagnosing skin rejection in vascularized composite allotransplantation: advances and challenges. *Clin Transplant*. 2014;28:277-285.
4. Thaunat O, Badet L, Dubois V, Kanitakis J, Petruzzo P, Morelon E. Immunopathology of rejection: do the rules of solid organ apply to vascularized composite allotransplantation? *Curr Opin Organ Transplant*. 2015;20:596-601.
5. Cendales LC, Kanitakis J, Schneeberger S, et al. The Banff 2007 working classification of skin-containing composite tissue allograft pathology. *Am J Transplant*. 2008;8:1396-1400.
6. Sarhane KA, Tuffaha SH, Broyles JM, et al. A critical analysis of rejection in vascularized composite allotransplantation: clinical, cellular and molecular aspects, current challenges, and novel concepts. *Front Immunol*. 2013;4:406.
7. Petruzzo P, Kanitakis J, Testelin S, et al. Clinicopathological findings of chronic rejection in a face grafted patient. *Transplantation*. 2015;99:2644-2650.
8. Kanitakis J, Petruzzo P, Gazarian A, et al. Capillary thrombosis in the skin: a pathologic hallmark of severe/chronic rejection of human vascularized composite tissue allografts? *Transplantation*. 2016;100:954-957.
9. Mundinger GS, Munivenkatappa R, Drachenberg CB, et al. Histopathology of chronic rejection in a nonhuman primate model of vascularized composite allotransplantation. *Transplantation*. 2013;95:1204-1210.
10. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*. 2014;14:272-283.