TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Alopecia areata in a composite tissue (hand) allograft recipient following graft rejection

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Alopecia areata (AA) is a form of nonscarring alopecia with a prevalence of 0.1–0.2% and a calculated lifetime risk of 2%, affecting an estimated 4.5 million people in the USA. Although its pathogenesis remains poorly known, it is believed to have an autoimmune origin, as suggested by its association with specific HLA alleles, presence of circulating autoantibodies (including to hair-follicle antigens), abnormalities in peripheral T-cell numbers and function, presence of infiltrates around the hair-follicle bulb (composed mainly of activated CD4+ T-cells and antigen-presenting cells), association with autoimmune diseases and response to immunosuppressive agents, including corticosteroids and cyclosporin A (CsA) [1]. The development of AA in organ-transplant recipients (OTR) receiving chronic immunosuppression is therefore unexpected, although it has been reported rarely following kidney/kidney-pancreas, liver, heart, haematopoietic and islet transplantation [2–4]. We report herein the first case of AA developing in a recipient of a composite tissue (double-hand) allograft.

A 24-year-old Caucasian man suffered at the age of 16 years bilateral forearm amputation because of an explosion. At the age of 21 years, he received a double-hand allograft from an 18-year-old brain-dead man with whom he had five HLA-mismatches. The induction immunosuppressive treatment (IST) included an association of thymoglobulin, prednisolone, tacrolimus and mycophenolate mofetil (MMF). The 1-year maintenance of IST included prednisone (5 mg/day), MMF (2 g/day) and tacrolimus (to obtain blood levels 5–10 ng/ml); the latter was converted to rapamycin (2 mg/day) on month 26 post graft because of renal toxicity. During follow-up, the patient developed three histologically confirmed episodes of graft rejection: the earlier ones (Banff grade I) manifested on day 10 and month 9 with erythematous-purpuric cutaneous micropapules; they were reversed with steroid boluses (250 mg) and/or an increase of oral steroid dose to 1 mg/kg (with progressive tapering to 5 mg/day). The third rejection (Banff grade III), developed during month 31 post graft and manifested with diffuse skin erythema limited to the allografted limbs (Fig. 1); it regressed over the following weeks with three corticosteroid boluses (1 g/day every other day) followed by an increase in oral steroids (as for the previous rejections) and topical applications of clobetasol and tacrolimus. One month following the last bolus, while receiving 20 mg/day prednisone and 2 mg/day rapamycin, the patient developed suddenly and with no obvious reason several 1–3 cm asymptomatic, noninflammatory, well-circumscribed patches of hair loss over the parietal and occipital scalp, typical of AA (Fig. 1). No family or personal history of AA was recalled. At the time of rejection, the patient had circulating anti-HLA class-I and -II antibodies; the latter included a donor-specific antibody (DSA) to HLA-DQ2. Three months after AA onset, the patient had merely circulating anti-HLA-class II antibodies (but no DSA). Daily applications of a hair-stimulating gel (rubefying gel, Ducray®) were prescribed; after 3 months some degree of hair regrowth was noted, but new alopecic plaques appeared on the beard.

This is the first report of AA in the setting of composite tissue allotransplantation (CTA). As AA is believed to be an autoimmune condition, its occurrence in OTR is puzzling, if not paradoxical, as the IST is expected to prevent the development of autoimmune diseases. Of note, the development of bullous pemphigoid, an autoimmune bullous dermatosis, has been recently reported in a double-hand allograft recipient [5]. On the other hand, independent of their immunosuppressive activity, both corticosteroids and CsA stimulate hair growth, often resulting in hirsutism, which may be cosmetically so bothersome that it motivates a change in therapy. At the time of AA development our patient was receiving corticosteroids, MMF and rapamycin, the latter in substitution of tacrolimus. The effect of tacrolimus on hair growth is controversial. Topical tacrolimus is not effective in the treatment of AA (probably because of poor percutaneous penetration). Conversion of CsA to tacrolimus improves hypertrichosis, and tacrolimus treatment in OTR has been associated with diffuse scalp alopecia; contrasting with these observations, one study found tacrolimus to be effective for the treatment of murine AA [6]. Our patient developed AA 3 months after tacrolimus discontinuation, so that the responsibility of this drug seems unlikely.

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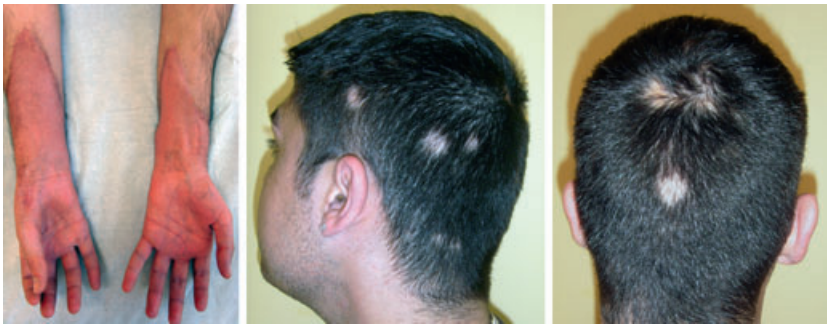

Figure 1. Left panel: rejection manifesting during month 31 post graft with diffuse erythema strictly limited to the allografted limbs. Middle & right panels: patches of alopecia areata over the temporal and occipital scalp.

Rapamycin has anti-angiogenic properties, therefore an adverse effect on hair growth, which is very sensitive to vascularization of the hair bulb, cannot be excluded. In renal-transplant patients receiving rapamycin-based IST diffuse mild alopecia occurs frequently, but AA is much rarer. The relationship between MMF and alopecia is also unclear. Although MMF has no effect on AA, in patients with lupus nephritis it is associated with a greatly reduced incidence of alopecia compared with cyclophosphamide. Corticosteroids administered either locally (with intralesional injections or under occlusive dressings) or as high-dose intravenous injection (500 mg methylprednisolone on three consecutive days) are often efficient for the treatment of AA [7]. Our patient developed AA 1 month after three steroid boluses, while he was under tapering regimen of oral prednisone following graft rejection.

Contrary to inner organs, rejection of skin-containing CTA can be observed by the patients, as it manifests with visible skin changes. Since AA can occasionally be triggered by emotional stress [8], we speculate that in our patient rejection caused sufficient stress to trigger AA, which was temporarily controlled by the steroid boluses given to reverse rejection, and appeared during steroid tapering.

The treatment of AA is challenging, especially in OTR who receive corticosteroid-based IST. Introduction of CsA may achieve hair regrowth, even in patients with pretransplant AA [9], however, the potential benefit of this drug should be carefully weighed against its side-effects. Local irritants (anthralin) may achieve partial hair regrowth [4]; minoxidil, a local vasodilator, can be used in association. However, AA may be self-limiting, even in OTR [10], so that treatment may be judged unnecessary.

Transplant physicians should be aware that despite the IST, OTR may develop autoimmune diseases, including AA, and should not misdiagnose the latter as other forms of circumscribed alopecia, namely tinea capitis, a fungal infection to which patients are exposed because of the immunosuppression. AA is diagnosed clinically; in case of doubt, mycological examination and/or skin biopsy should be performed to avoid erroneous diagnoses and inappropriate treatment.

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References

1. Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med* 2012; **366**: 1515.
2. Phillips MA, Graves JE, Nunley JR. Alopecia areata presenting in 2 kidney-pancreas transplant recipients taking cyclosporine. *J Am Acad Dermatol* 2005; **5** (Suppl. 1): S252.
3. Sanli H, Kusak F, Arat M, Ekmekci P, Ilhan O. Simultaneous onset of chronic graft versus host disease and alopecia areata following allogeneic haematopoietic cell transplantation. *Acta Derm Venereol* 2004; **84**: 86.
4. Zuk DM, Koh A, Imes S, Shapiro AM, Senior PA. Three cases of alopecia following clinical islet transplantation. *Am J Transplant* 2011; **11**: 163.

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5. Weissenbacher A, Hautz T, Zelger B, *et al.* Bullous pemphigoid eleven years after bilateral hand transplantation. *Am J Transplant* 2012; **12**: 1064.
6. Freyschmidt-Paul P, Ziegler A, McElwee KJ, *et al.* Treatment of alopecia areata in C3H/HeJ mice with the topical immunosuppressant FK506 (Tacrolimus). *Eur J Dermatol* 2001; **11**: 405.
7. Luggen P, Hunziker T. High-dose intravenous corticosteroid pulse therapy in alopecia areata: own experience compared with the literature. *J Dtsch Dermatol Ges* 2008; **6**: 375.
8. García-Hernández MJ, Ruiz-Doblado S, Rodriguez-Pichardo A, Camacho F. Alopecia areata, stress and psychiatric disorders: a review. *J Dermatol* 1999; **26**: 625.
9. Mannes GP, van der Bij W, de Boer WJ, Blanken R. Delightful hair growth after lung transplantation. *Transpl Int* 1995; **8**: 247.
10. Euvrard S, Kanitakis J, Cochat P, Cambazard F, Claudy A. Skin diseases in children with organ transplants. *J Am Acad Dermatol* 2001; **44**: 932.

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