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CASE STUDY

Resolution of Severe Atopic Dermatitis After Tacrolimus Withdrawal

Gaston M. Ponte,*[1] David A. Baidal,*[1] Paolo Romanelli,† Raquel N. Faradji,*‡ Raffaella Poggioli,* Pablo Cure,* Tatiana Froud,*§ Gennaro Selvaggi,*§ Antonello Pileggi,§ Camillo Ricordi,*§ and Rodolfo Alejandro*‡

*Diabetes Research Institute, University of Miami Leonard M. Miller School of Medicine, Miami, FL 33136, USA
†Department of Dermatology and Cutaneous Surgery, University of Miami Leonard M. Miller School of Medicine, Miami, FL, 33136, USA
‡Department of Medicine, University of Miami Leonard M. Miller School of Medicine, Miami, FL 33136, USA
§DeWitt Daughtry Family Department of Surgery, University of Miami Leonard M. Miller School of Medicine, Miami, FL 33136, USA

Tacrolimus is an immunosuppressive agent used in solid organ and islet transplantation. Its topical form has shown benefit in the treatment of inflammatory skin conditions. Although tacrolimus has a wide spectrum of side effects, dermatological complications related to systemic tacrolimus therapy are limited in the literature. Atopic dermatitis (AD) is a chronic pruritic cutaneous condition that usually begins in infancy and is characterized by an increased Th2 response. We report the case of a patient with type 1 diabetes mellitus (T1DM) and history of AD latent for 10 years who developed severe dermatitis and alopecia 5 months after undergoing allogeneic islet transplantation and initiating a steroid-free immunosuppressive regimen with sirolimus and tacrolimus maintenance. After exclusion of other possible causes for the progression and exacerbation of the clinical presentation of AD, discontinuation of tacrolimus and introduction of mycophenolate mofetil resulted in full remission of the symptoms. The beneficial effects of tacrolimus withdrawal suggest a cause–effect relationship between this adverse event and the utilization of the drug. Islet graft function remained stable after modification of the therapeutic regimen (stable glycemic control and unchanged C-peptide).

Key words: Atopic dermatitis; Alopecia areata; Diabetes; Immunosuppression; Islet transplantation; Tacrolimus

INTRODUCTION

Transplantation of allogeneic islets is currently limited to patients with type 1 diabetes mellitus (T1DM) with hypoglycemia unawareness and unstable glycemic control (8,24,34,40,45,47,48,52,56,57). The most remarkable benefits of islet transplantation include improved glycemic control (with normalization of glycated hemoglobin A1c and reduction of glycemic excursion throughout the day) (20) and prevention of severe hypoglycemic episodes (1,40,51,53), even when exogenous insulin is required (i.e., marginal islet graft function) (8,24,34,40, 45,47,48,52,56,57). Improved health-related (5) and diabetes quality of life (41) is commonly observed in patients with T1DM after islet transplantation, which is the direct consequence of improved glycemic control and reduced fear of hypoglycemia.

The steady progress of the islet transplantation field has led to increased success both in islet cell processing and clinical outcome in recent years (37,45). Very promising approaches are under development aiming at improving the efficiency of organ recovery and islet isolation techniques (6,15,19,50,54,59,63,67), enhancing engraftment through cytoprotection of islet grafts (27,28,35, 38,68), islet implantation into alternative sites (7,23,39), implementation of immunomodulatory (38,43) and im-

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[1]These two authors contributed equally to this report.
Address correspondence to Rodolfo Alejandro, M.D., Diabetes Research Institute (R-134), 1450 NW 10th Avenue, Miami, FL 33136, USA. Tel: (305) 243-5324; Fax: (305) 243-1058; E-mail: ralejand@med.miami.edu

munoisolation (30,31) protocols to reduce the need for chronic immunosuppression (47). Meanwhile, increasing efforts have been focused toward the identification of safe and unlimited alternative sources of insulin-producing cells to overcome shortage of deceased donor pancreata for transplantation in the near future (2,13,14, 42,49).

The standard maintenance immunosuppressive (IS) regimen for current clinical islet transplantation was introduced as the "Edmonton protocol" and consists of a steroid-free regimen based on sirolimus and tacrolimus (56), which has contributed to the unprecedented success rates of allogeneic islet transplantation reported by multiple centers worldwide in recent years (8,20,24, 34,40,45,47,48,52,56,57).

A number of untoward effects (11,17,21,25,29, 32,36,52,55,57,61), including cutaneous complications, have been associated with the use of these drugs (21,33). In particular, mild (e.g., acne-like eruptions and scalp folliculitis) to severe (e.g., epistaxis, angioedema, and mucous membrane disorders, including aphthous stomatits) dermatological complications have been reported in association with sirolimus treatment (33), requiring drug withdrawal in severe cases. However, dermatological complications related to oral tacrolimus are scarce in the literature (12,66).

Herein, we report a case of dermatological changes consistent with atopic dermatitis (AD) and a diffuse variant of alopecia areata (AA) in a recipient of allogeneic islets that resolved after tacrolimus withdrawal.

MATERIALS AND METHODS

A C-peptide-negative, 43-year-old Caucasian female with T1DM of 37 years duration complicated by stable proliferative retinopathy, hypoglycemia unawareness, and unstable glycemic control received allogeneic islets as part of an ongoing Islet Transplantation Alone (ITA) trial at our center (17,40). Medical history was relevant for fibrocystic breast disease, pyelonephritis, seizure disorder (stable and treated with carbamazepine), and mild intermittent AD, which had been latent for 10 years prior to enrollment for ITA. Pretransplant weight was 57 kg and height was 155 cm, with a corresponding BMI of 23.7 kg/m^2. Pretransplant insulin requirements and hemoglobin A1c were 31 U daily (0.54 U/kg/day) and 8.6%, respectively. Liver and renal function tests, chemistries, and lipid profile were all within normal range (Table 1).

Islets were isolated at the Human Cell Processing Facility of the Diabetes Research Institute and were obtained from human pancreata recovered from multiorgan donors after cerebral death. A modification of the automated digestion method followed by density gradient purification was used (15,26,46). Islets were then transplanted intrahepatically by percutaneous catheterization of the portal vein using the bag technique (3,18).

Immunosuppression was started on the day before the first islet infusion [postoperative day (POD) −1], and consisted of tacrolimus (Prograf®, Astellas Pharma US, Inc.) target trough level 4–6 ng/ml, and sirolimus (Rapamune®, Wyeth, Pharmaceuticals, Inc., Madison, NJ, USA) target trough level 12–15 ng/ml for 3 months, 10–12 ng/ml thereafter. A five dose induction course of daclizumab (Zenapax®, Roche, NJ, USA) 1 mg/kg biweekly was given starting from the day of each islet infusion followed by monthly and bimonthly administration for the first and second years posttransplant, respectively (17). The patient also received induction treatment with infliximab (Remicade®, Centocor, Malvera, PA, USA) 2 h prior to the islet infusion at a dose of 5 mg/kg for the first infusion and 10 mg/kg for the third infusion (17).

Valgancyclovir (Valcyte®, Roche Pharmaceuticals, Nutley, NJ, USA) 900 mg daily for 3 months after each islet infusion was given for prophylaxis against cytomegalovirus (4,10,17,22), and trimethroprim/sulfamethoxazole (TMP-SMX) 80/400 mg three times a week indefinitely for *Pneumocystis jiroveci* pneumonia prophylaxis (17).

Case Presentation

The patient received a total of three intraportal infusions of allogeneic islets between July 2001 and July 2003. With the first infusion, 468,867 islet equivalents (IEQ) (8226 IEQ/kg) were transplanted leading to a 55% reduction in insulin requirements (17). On POD 22, the patient received a second islet infusion of 580,070 IEQ (10,177 IEQ/kg), achieving insulin independence immediately following the infusion. The patient continued with stable islet graft function and stable glycemic control in spite of having required insulin reintroduction on POD 208 (5 U/day).

Five months after islet transplantation (POD 142), the patient developed a mild, intermittent rash characterized by small red maculae and vesicles located on the palms of her hands and accentuated palmar creases. During this time, sirolimus and tacrolimus levels were 11.5 ± 3 and 5.2 ± 0.2 ng/ml ($n = 3$), respectively. Due to its mild presentation, the patient did not report symptoms until POD 289. By then, the rash had involved the upper back following a patchy distribution with associated mild pruritus. Due to the intermittent and mild nature of the symptoms, no treatment was initially installed. By POD 362 (approximately 1 year from the first islet transplant), the rash had spread to the dorsal aspect of hands, wrists,

forearms, and popliteal fossae, and the pruritus was aggravated by perspiration and contact with hot water. Throughout this time, levels of sirolimus and tacrolimus were 10.1 ± 1.0 and 4.9 ± 0.5 ng/ml ($n = 3$), respectively. Based on the clinical presentation and the patient's past medical history a presumptive diagnosis of AD was ascertained on POD 374. Topical fluticasone propionate cream 0.05% (Cutivate®, GlaxoSmithKline, Pittsburg, PA, USA) was then implemented, which improved the pruritus with little effect on the rash. Notably, oral steroids were avoided as first line of intervention in order to prevent alterations in glycemic control. By POD 480, the eczematous rash had spread to the axillae, flanks, back, and legs and the therapeutic regimen was modified by replacing the steroid cream with a topical calcineurin inhibitor, pimecrolimus cream 1% (Elidel®, Novartis pharmaceuticals Corp, East Hanover, NJ, USA). Trough levels of sirolimus and tacrolimus were 12.8 ± 2.4 and $5.1\& \pm 0.3$ ng/ml ($n = 3$), respectively.

Within a month (POD 512), a rise in the eosinophil counts (10.4% vs. baseline <6.0%) was noted and paralleled by progression of the eczematous rash that comprised the face, and by worsening of the pruritus affecting the patient's sleeping pattern. Despite transient improvement of symptoms with topical treatment and oral antihistaminic agents, the skin lesions continued to flare. Phototherapy was started on POD 603 consisting of exposure of the affected skin areas to ultraviolet B (UVB) radiation twice a week for 30 days but resulted in minimal clinical improvement. Levels of sirolimus and tacrolimus were 12.4 ± 1.3 and 5.1 ± 0.5 ng/ml ($n = 3$), respectively.

In order to exclude a possible drug reaction secondary to the use of TMP-SMX, antibiotic prophylaxis was modified by replacing TMP-SMX for dapsone 100 mg twice weekly. Symptoms did not improve following this change and dapsone was discontinued after 2 weeks and TMP-SMX reintroduced.

A supplemental islet infusion was performed on POD 715 due to deteriorated glycemic control that had led to reintroduction of insulin. A total of 802,632 IEQ (15,737 IEQ/kg) were infused. Insulin independence was regained approximately 3 months following this islet infusion (POD 796). At this time, levels of sirolimus and tacrolimus were 13.3 ± 1.3 and 4.1 ± 0.3 ng/ml ($n = 3$), respectively.

The patient subsequently reported mild hair loss on POD 878 and physical examination revealed small areas of alopecia on the scalp, eyebrows, pubic, and axillary regions, and ill-defined pink plaques with overlying scales and lichenification on the face, trunk, and extremities. Xerosis was also observed on both hands as well as dry cracked cuticles on all digits. Eosinophil count was elevated at 26%. Punch skin biopsies were obtained from the right forearm, right wrist, and right clavicular areas. Pathological examination revealed loss of the stratum corneum and granular layer with moderate spongiosis and superficial and deep perivascular and periadnexal chronic inflammation with admixed neutrophils, eosinophils, and hemorrhage (Fig. 1). All medications, except for sirolimus, tacrolimus, and carbamazepine, were discontinued. During this time, sirolimus and tacrolimus levels were 12.3 ± 3.2 and 4.7 ± 0.8 ng/ml ($n = 3$), respectively. The clinical symptoms did not improve after this intervention, suggesting a possible role of the IS drugs in the exacerbation of the eczematous rash. Before altering the maintenance IS regimen that could have resulted in islet allograft dysfunction, a short course of oral steroid treatment was started on POD 973 (25-day course of prednisone starting at 40 mg daily for 5 days, followed by tapering every 5 days to 30, 20, 10, and 5 mg, respectively). Pruritus initially resolved under treatment, but reappeared when the steroid dose was tapered to 20 mg/day, and the clinical picture worsened shortly after discontinuation of prednisone with severe pruritus and the alopecia comprising most of the scalp (Fig. 2A1, A2). Levels of sirolimus and tacrolimus during this time were 9.1 ± 0.7 and 3.6 ± 1.4 ng/ml ($n = 3$), respectively.

The IS regimen was then modified on POD 1012 by the introduction of mycophenolate mofetil (MMF; Cellcept®, Roche Laboratories Inc., Nutley, NJ, USA) followed by weaning from tacrolimus. MMF was introduced at a dose of 250 mg PO bid and increased by 250 mg bid every 4 days until achieving a target total dose of 2000 mg/day. Four days after achieving target dose of MMF, tacrolimus was reduced by 0.5 mg every 2 days starting with the evening dose and alternating with the morning dose until discontinuation 2 weeks later. Within 2 weeks from tacrolimus withdrawal, the patient reported a significant improvement of both the rash and pruritus (Fig. 2B1, B2). The patient continued with stable islet graft function demonstrated by C-peptide levels and insulin independence 3 months after tacrolimus to MMF conversion. On POD 1118, the patient required reintroduction of insulin (~6 U/day). Approximately 5 months post-tacrolimus-to-MMF conversion (POD 1194) pruritus had resolved, skin lesions were almost completely healed, eosinophil count returned to baseline, and no areas of alopecia were evident (Fig. 2C1, C2). Throughout this time, levels of sirolimus were 11.9 ± 5.1 ng/ml ($n = 3$). The active form of MMF, which is mychophenolic acid (MPA), was gathered for assessment of drug trough levels; however, the target for this agent was the maximal tolerated dose without experienc-

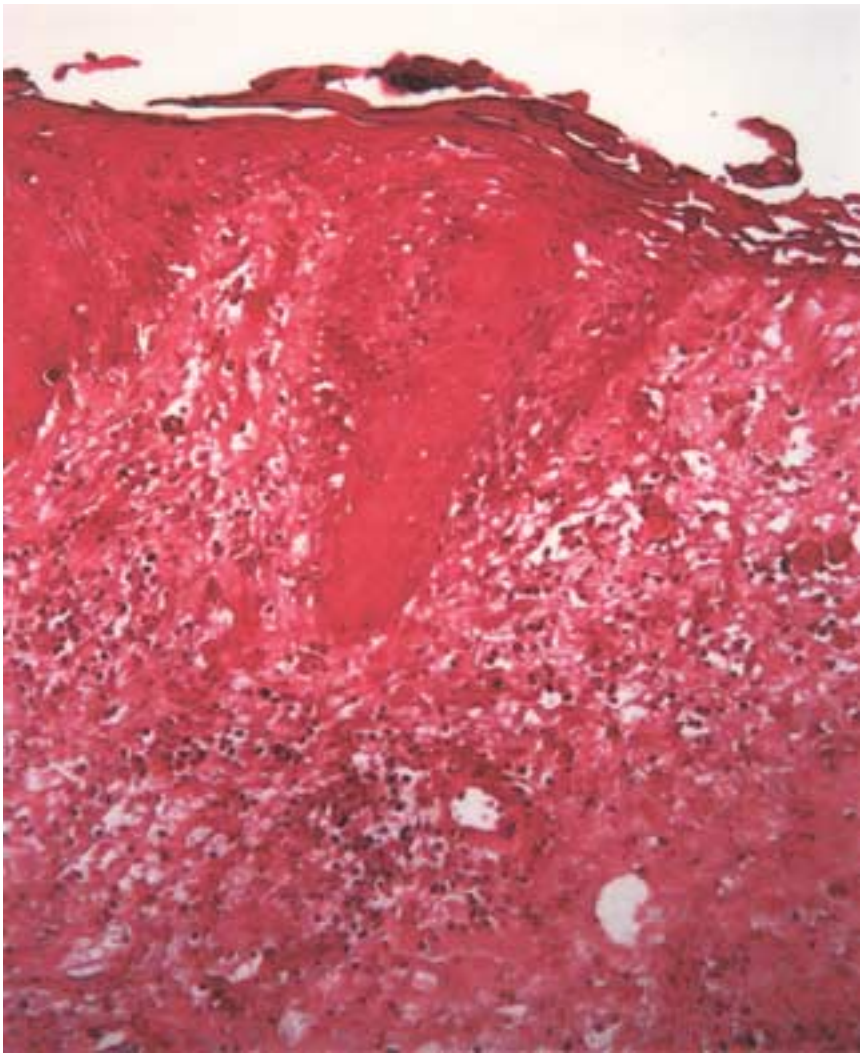

Figure 1. Skin biopsy right clavicle area (POD 890). Epidermis demonstrates loss of stratum corneum and granular layer with moderate spongiosis and superficial and deep perivascular and periadnexal chronic inflammation with admixed neutrophils, eosinophils, and hemorrhage. Steiner stain was performed and was negative for spirochetes (20× magnification).

Table 1. Patient Data During Follow-up

	POD 0 (Before Transplant)	POD 960 (Preconversion)	POD 1240 (Postconversion)
Insulin requirements (units/kg/day)	0.54	0.00	0.04
A1c (%)	7.7	5.8	6.0
C-Peptide (ng/ml)	0.10	1.00	1.70
C-Peptide/glucose ratio	<0.0	0.92	0.85
WBC (×1000 cell/cc)	7070	3500	4200
Hbg	13.6	9.5	11.6
Hct	41.0	29	34.70

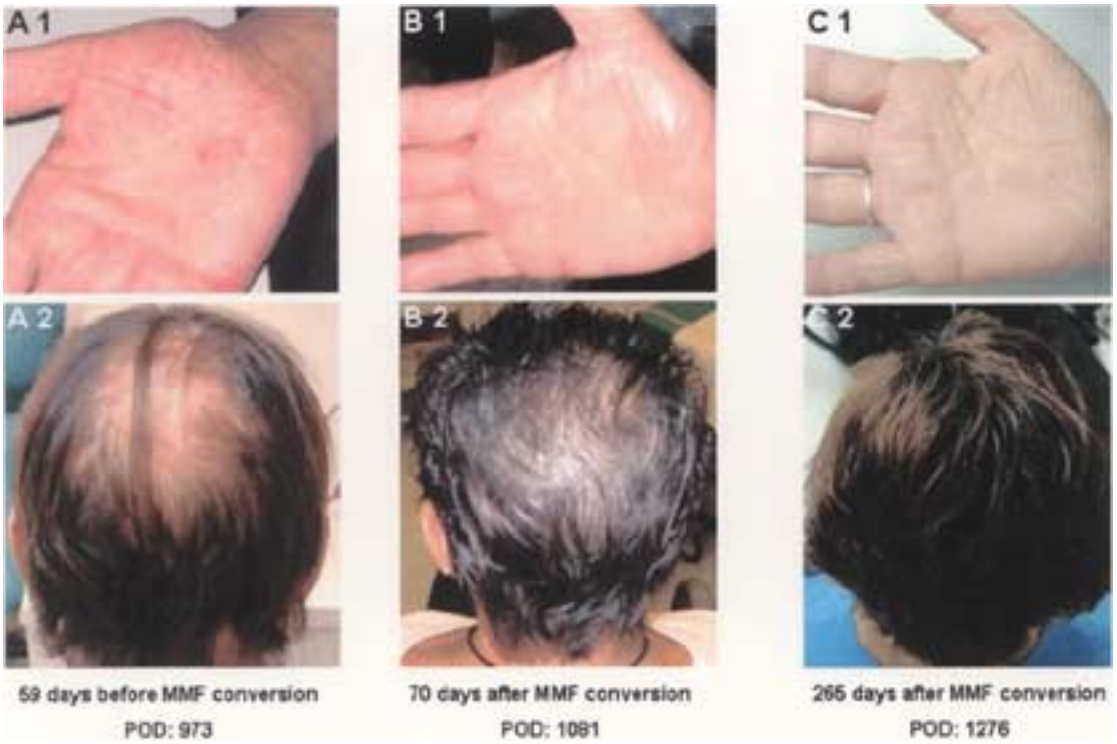

Figure 2. Dermatological changes observed. (A1, A2) Eczematous changes and alopecia areata at POD 973. (B1, B2) Improvement in eczematous changes and partial recovery of hair growth and hair thickness at POD 1081. (C1, C2) Near resolution of eczematous changes with minimal xerosis and complete hair growth recovery at POD 1276.

ing an adverse reaction. Due to persistent diarrhea from the use of MMF the patient was subsequently changed to the enteric coated form of MPA (Myfortic®, Novartis, East Hanover, NJ, USA) with resolution of symptoms.

Seven months after withdrawal of tacrolimus (POD 1244), the patient continued with stable islet graft function demonstrated by C-peptide levels (1.7 ng/ml) and stable glycemic control (Table 1). During this time, levels of sirolimus and MPA were 9.4 ± 3.1 and 2.1 ± 1.2 ng/ml ($n = 3$), respectively.

DISCUSSION

Atopic dermatitis (also called atopic eczema) is an inflammatory skin disorder characterized by recurrent episodes of inflamed, dry, often extremely pruritic, and scaling skin (30). Infants may have a predilection for occurrence on the cheeks. Children, adolescents, and adults have lesions on flexural surfaces, the neck, eyelids, and behind the ears. Acute episodes are primarily managed with topical corticosteroids (58,65).

In AD the response to common allergens leads to generation of T-helper (Th)-2 lymphocytes in preference of Th-1 (16). Th-2 cells produce mainly IL-4 and IL-5, which regulate IgE production, mast cells, and eosinophils (44,60,62,64). Similarly, patients with alopecia areata present with significant cytokine elevation and humoral response (44,62).

In the clinical case presented herein, AD had been latent for 10 years prior to enrollment in the study and reappeared approximately 5 months after islet transplantation. After ruling out other possible causes, immunosuppression was considered the most probable cause for the exacerbation of AD symptoms in our patient. Notably, dermatological complications have been described with the use of immunosuppression consisting of tacrolimus and/or sirolimus (21,33,62). Although the mechanism by which immunosuppression led to this clinical picture is unclear, the effect on Th-1 and Th-2 responses may have contributed to it. Weimer et al. evaluated the effects in the Th-1, Th-2, and monokine responses resulting from switching cyclosporine to tacrolimus in 20 renal transplant recipients and found a significantly decreased expression in costimulatory ligands and adhesion molecules on T cells (namely, CD28, CD40L, and CD54), B cells (CD40), and monocytes (CD40) (64). Although B7-1 (CD80) expression on monocytes was not suppressed, the marked reduction in CD28 on T cells coincided with decreased PHA-stimulated IL-2 secretion by T-lymphocytes and with decreased expression of

CD25 on B-cells (64). On the other hand, despite a decreased expression in CD40 and CD40L, Th-2 responses (IL-4, IL-10) were not affected and there was even an increased IL-10 response (64). These data suggest an inhibition of the Th-1 response with unaffected Th-2 responses with the use of tacrolimus. Although not formally addressed in our study, it could be hypothesized that inhibition of the Th-1 response by tacrolimus may have favored a shift of the immune response toward the Th-2 pathway in our patient with past history of AD. The effects of this shift may have contributed to the development of an increased humoral response resulting in the recurrence and exacerbation of this patient's AD.

Interestingly, topical calcineurin inhibitors (pimecrolimus and topical tacrolimus-protopic) are approved for the treatment of AD and may also have a beneficial role in treatment of alopecia (12). However, topical treatment with pimecrolimus was unsuccessful on this patient.

The alopecia observed in this patient was initially in the form of small circular patches with intact underlying skin limited to the parietal area of the scalp. Within a short period of time, new areas of alopecia appeared and coalesced. As the condition progressed, the eyebrows, axillary, and pubic areas were also compromised, resulting in almost complete hair loss. Androgenetic alopecia or common baldness usually develops within the second to third decade of life. It is a slowly progressive irreversible condition affecting the scalp and has a hormonal (dihydrotestosterone) and genetic component (9). Alopecia areata is an autoimmune disorder affecting the hair follicle and is characterized by hair loss that occurs in scattered patches on the scalp. Although some patients may lose all scalp (alopecia totalis) and body hair (alopecia universalis), the condition is potentially reversible (9).

The presentation in our patient also suggests a diagnosis of alopecia areata. The compromise of the eyebrows and axillary and pubic areas resembles the pattern of alopecia universalis, a diffuse variant of alopecia areata. In addition, the restoration of hair growth in the affected areas following discontinuation of tacrolimus rules against androgenetic alopecia, an irreversible condition.

Severe skin disorders have been reported in kidney transplant recipients receiving sirolimus treatment and an association with our patient's rash cannot be completely ruled out.

CONCLUSIONS

In summary, we report a case of tacrolimus-induced severe flaring AD with alopecia areata in a patient with T1DM following IS treatment for islet transplantation who presented with previous history of AD in remission for approximately 10 years prior to ITA. After exclusion of other possible causes for the progression and exacerbation of the clinical presentation, tacrolimus withdrawal resulted in full remission to pretransplant status and recovery of hair growth. The beneficial effects of tacrolimus withdrawal suggest a cause–effect relationship between this adverse event and the utilization of the drug (Fig. 2). Conversion of the maintenance IS to MMF and sirolimus not only resolved the AD symptoms and alopecia, but it also dramatically improved the patient's quality of life (41) and sustained islet allograft function demonstrated by stable glycemic control.

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