

Paradoxical eczema in infants after heart transplantation

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Abstract

New-onset psoriasis in patients receiving tumor necrosis factor inhibitors is well recognized in children and adults. We describe three children who underwent cardiac transplantation and developed an analogous form of paradoxical eczema occurring 2–48 months after starting systemic tacrolimus, a drug widely used topically to treat eczema. Anecdotal reports and our experience suggest that tacrolimus taper with alternative systemic antirejection immunosuppressant may lead to skin clearance. Pending additional insight, treatment should include optimizing skin barrier function, minimizing microbial and allergic triggers, and coordinating care to choose the best-tolerated systemic immunosuppressant regimen at the lowest effective dose.

KEYWORDS

eczema, genetic disease/mechanism, immunodeficiency, systemic therapy, topical therapy

1 | INTRODUCTION

Paradoxical psoriasis triggered by tumor necrosis factor (TNF) inhibitors has been reported in children and adults.¹ We report an analogous form of eczema occurring in children who underwent cardiac transplantation taking systemic antirejection therapy featuring the calcineurin inhibitor tacrolimus. Tacrolimus is used systemically to prevent solid organ rejection but also topically to control atopic dermatitis. Several reports have associated systemic tacrolimus with food allergy, asthma, eosinophilia,^{2–4} and, paradoxically, eczema.^{5–7} One proposed mechanism for tacrolimus-associated atopy is suppression of Th1 lymphocytes through interleukin (IL)-2 deprivation, leading to Th2-biased immunity.^{4,5} We present three children undergoing systemic immunosuppression with tacrolimus after cardiac transplantation in infancy who developed paradoxical eczema. Oral tacrolimus taper in two children resulted in significant improvement or skin clearance.

2 | CASE REPORTS

The Institutional Review Board at Saint Louis University School of Medicine approved this retrospective database review. The patients were seen at Cardinal Glennon Children's Hospital Dermatology Clinic between 2005 and 2013.

2.1 | Patient 1

Patient 1 underwent cardiac transplantation at 1 month of age for pulmonary atresia with intact intraventricular septum, hypoplastic right heart, and right ventricle-dependent coronary arteries. He was started on systemic immunosuppression with oral tacrolimus (0.14 mg/kg/d, adjusted to goal serum trough 8–10 ng/mL) and mycophenolate mofetil (10–15 mg/kg/d), followed by worsening eczema that prompted dermatology evaluation at 10 months (Table 1). His history and examination were remarkable for recurrent cutaneous and extracutaneous infections, developmental and language delay, and dysmorphic features, including bilateral hair whorls, high arched palate, and notched superior helices suggestive of DiGeorge-velocardiofacial syndrome (DGS-VCFS), although fluorescence in situ hybridization (FISH) testing was negative. Recurrent otitis media and sinusitis were controlled using daily cefdinir prophylaxis. Bland emollients, bleach baths, ketoconazole shampoo, and intermittent mometasone 0.1% ointment improved his skin but did not mitigate frequent flares. Serial surveillance skin and throat cultures identified colonization with group A *Streptococcus* (GAS) and methicillin-resistant *Staphylococcus aureus*, addressed with tonsillectomy and adenoidectomy at age 29 months. His skin disease stabilized for 16 months with adjunctive pimecrolimus 1% cream, monthly mupirocin decolonization, and ciclopirox shampoo, but subsequently worsened, requiring hospitalization for intensive skin care. Herpes simplex

virus polymerase chain reaction and viral cultures were negative, but high immunoglobulin (IgM and IgG titers suggested eczema herpeticum incognito.⁶ Therapeutic intravenous acyclovir followed by daily prophylactic valacyclovir failed to achieve control. Skin biopsy to exclude graft-versus-host disease found only nonspecific findings of psoriasiform dermatitis and a subcorneal pustule with Gram-positive cocci. Immune evaluation revealed persistent eosinophilia; mildly high total IgE; pan-positive 12-panel cytokines; and low complement, lymphocyte counts, and proliferative responses (Table 2). A trial of monthly intravenous immunoglobulin (IVIG) yielded some improvement, but was discontinued after routine surveillance cardiac biopsy showed mild evidence of graft rejection. The addition of sirolimus (1 mg/m²/d, adjusted to goal serum trough 5-10 ng/mL) and prednisolone (0.4-0.8 mg/kg/d) led to temporary skin improvement, followed by recurrent skin flares requiring hospitalization. After his fourth hospitalization for flaring skin disease in 12 months, his oral tacrolimus dose was reduced by more than half (0.077 mg/kg/d), followed by immediate improvement in his skin disease (Figures 1-3). Tacrolimus was subsequently decreased to 0.037 mg/kg/d (73% reduction), with plans for complete withdrawal. He remains on mycophenolate mofetil (15 mg/kg/d), sirolimus (1 mg/m²/d, adjusted to goal serum trough 5-10 ng/mL), and prednisolone (0.36 mg/kg/d) without evidence of transplant rejection and continues to use mometasone 0.1% ointment every other day to manage his skin disease.

2.2 | Patient 2

Patient 2 was 3 months old at the time of cardiac transplantation for critical aortic stenosis and hypoplastic left heart after a failed Norwood procedure. He developed worsening dermatitis between 4 and 6 years of age while on maintenance immunosuppression with oral tacrolimus (0.18 mg/kg/d) and azathioprine (1.5 mg/kg/d). He presented to dermatology at age 7 years after several courses of amoxicillin with clavulanic acid for presumed skin infection. He subsequently underwent tonsillectomy and adenoidectomy for recurrent sinusitis and otitis media. DGS-VCFS was suspected on the basis of recurrent infections, developmental delay, and feeding difficulty requiring a gastrostomy tube until age 5 years, but FISH testing was negative. Bland skin care plus mometasone 0.1% ointment failed to control skin flares. Serial surveillance skin and throat cultures identified GAS and methicillin-sensitive *S. aureus* colonization. Evaluation of serum allergen-specific IgE revealed high titers to multiple allergens (dog, cat, strawberry, dust mite, egg). Home allergen (dog) removal and mometasone ointment led to temporary skin clearing, but he continued to have frequent flares treated with amoxicillin with clavulanic acid, topical mupirocin or retapamulin, and tacrolimus 0.01% ointment. Further immune evaluation was remarkable for low T- and B-cell mitogen responses and low postimmunization *Hae-mophilus influenzae* type B and pneumococcal titers, which increased

TABLE 1 Management and outcomes of reported cases

Patient	Age at transplantation, mo	Age at eczema onset	Maintenance antirejection therapy at eczema onset	Therapeutic approach ^a (plus standard skin care ^b)	Antirejection therapy at publication	Eczema control
1	1	6 mo	Tacrolimus 0.14 mg/kg/d, adjusted to serum trough 8-10 ng/mL; mycophenolate mofetil 10-15 mg/kg/d	Mometasone ointment 0.1%, pimecrolimus CR 1%, wet wraps, ciclopirox CR, mupirocin prophylaxis, trimethoprim/sulfamethoxazole or cefdinir prophylaxis; valacyclovir; nystatin; IVIG, salicylic 1% solution; tonsillectomy and adenoidectomy; hospitalized 4 times for intensive skin care ^b	Tacrolimus 0.037 mg/kg/d; mycophenolate mofetil 15 mg/kg/d; sirolimus 1 mg/m ² /d ^c ; prednisolone 0.36 mg/kg/d ^c	Improved after systemic tacrolimus dose reduction
2	3	4 y	Tacrolimus 0.18 mg/kg/d; azathioprine 1.5 mg/kg/d	Mometasone ointment 0.1%, fluticasone ointment 0.005%, tacrolimus ointment 0.03%, mupirocin prophylaxis; tonsillectomy and adenoidectomy	Sirolimus 0.6-1 mg/m ² /d ^d ; mycophenolate mofetil 28-36 mg/kg/d ^d	Cleared after systemic tacrolimus discontinuation
3	3	5 mo	Tacrolimus 0.2-0.26 mg/kg/d, adjusted to goal serum trough 8-10 ng/mL; mycophenolate mofetil 20-26 mg/kg/d	Fluticasone ointment 0.005%, pimecrolimus CR 1%, calcipotriol ointment	Tacrolimus 0.2 mg/kg/d, adjusted to goal serum trough 8-10 ng/mL; mycophenolate mofetil 20 mg/kg/d	Marginally controlled on intermittent fluticasone ointment 0.005% and calcipotriol

^aNot all medications in therapies column initiated simultaneously. Semicolons indicate where new medications were added to or replaced existing regimen.

^bDefined as emollients, bland skin care, bleach baths, allergen avoidance or removal, ketoconazole shampoo.

^cSirolimus and prednisolone added 3 y after transplantation, after signs of rejection following administration of intravenous immunoglobulin (IVIG) for skin disease flare.

^dSirolimus and mycophenolic acid added 10 y after transplantation after posttransplantation lymphoproliferative disease. CR, controlled release.

TABLE 2 Microbial and immunologic characteristics of reported cases

Patient	Microbial triggers ^a	Recurrent extracutaneous infections	IgE	Remarkable immune laboratory results ^b
1	Skin and perianal <i>Streptococcus</i> carriage; nares methicillin-resistant <i>Staphylococcus aureus</i> carriage; negative serial yeast, fungal smears, cultures, HSV polymerase chain reaction and cultures; positive HSV IgM and IgG	Otitis media, sinusitis	High total IgE - 126 IU/mL (18 mo) - 132 IU/mL (3 y) Specific IgE positive to egg white, cow milk, peanut	Low complement ^c ; low lymphocyte counts and proliferative responses ^d ; high 12-panel cytokines ^e ; eosinophilia ^f
2	Throat, scalp, and skin <i>Streptococcus</i> and methicillin-susceptible <i>Staphylococcus aureus</i> colonization	Otitis media, sinusitis	High total IgE - 17,216 IU/mL (6 y) - 4,385 IU/mL (9 y) Specific IgE positive to egg, dog, cat, strawberry, dust mite	Low lymphocyte proliferative responses ^g ; eosinophilia ^h
3	Negative throat and skin microbial carriage; negative skin fungal cultures	None	Normal total IgE - 4 IU/mL (17 mo) - 3 IU/mL (15 mo) Allergen-specific IgE negative	Eosinophilia ⁱ

^aCarrier status defined as three positive cultures within 6 mo.

^bImmune laboratory tests were performed while patients were undergoing systemic antirejection therapy and, in the case of patient 1, before intravenous immunoglobulin (IVIG) administration.

^cLow C1R and CH50 (total) complement levels; normal C1Q, C1 functional, C2, C3, C4 levels; normal AH50 level (ARUP Laboratories, Salt Lake City, UT, USA).

^dAbsent responses to *Candida* and tetanus antigen (Ag); normal responses to phytohemagglutinin (PHA), pokeweed mitogen (PWM), Concanavalin A (ConA), alloAg (Pediatric Allergy & Immunology Laboratory, School of Medicine, St. Louis University, St. Louis, MO, USA).

^eElevated interleukin (IL)-2, IL-2R (sol), IL-12, interferon gamma, IL-4, IL-5, IL-10, IL-13, IL-1B, IL-6, IL-8, tumor necrosis factor alpha (ARUP Laboratories).

^fEosinophilia $5.45 \pm 3.19\%$, range 0.3–14.2% (normal < 7%); Absolute (ABS) $530 \pm 370/\mu\text{L}$, range 20–1540/ μL (normal 30–530/ μL).

^gLow responses to phytohemagglutinin PHA, phorbol 12-myristate 13-acetate PMA (Pediatric Allergy & Immunology Laboratory).

^hEosinophilia $4.16 \pm 3.22\%$, range 2.3–13.1% (normal < 7%); ABS $340 \pm 270/\mu\text{L}$, range 70–1220/ μL (normal 30–530/ μL).

ⁱEosinophilia $7.02 \pm 3.03\%$, range 4–15.6% (normal < 7%); ABS $480 \pm 260/\mu\text{L}$, range 120–1,250/ μL (normal 30–530/ μL).

HSV, herpes simplex virus.

after reimmunization. Posttransplantation lymphoproliferative disease and recurrent eczema at age 9 years complicated his subsequent course. At that time, oral tacrolimus was discontinued and prednisone started. Four months later he was transitioned from prednisone to mycophenolate mofetil (28–36 mg/kg/d). Sirolimus (0.6–1 mg/m²/d) was added after an additional 8 months. After tacrolimus was discontinued, his eczema cleared, and he has remained clear off prednisone and topical treatment for 4 years. His lymphoproliferative disease is in remission and cardiac function is stable.

2.3 | Patient 3

Patient 3 was 3 months old at the time of cardiac transplantation for pulmonary atresia with intact ventricular septum, coronary artery abnormality, and right ventricle-dependent coronary circulation. He was started on a maintenance antirejection regimen of oral tacrolimus (0.2–0.26 mg/kg/d, adjusted to goal serum trough 8–10 ng/mL) plus mycophenolate mofetil (20–26 mg/kg/d) and developed dermatitis 2 months later that failed to respond to hydrocortisone valerate 0.2% cream. He presented to the dermatology clinic at age 11 months with generalized eczema and a history of recurrent otitis

media and upper respiratory infections. Physical examination identified a high arched palate and notched superior helices, but FISH for DGS-VCFS was negative. Evaluation for an identifiable allergen or microbial trigger was negative. Serial blood cell counts over 3 years showed episodic eosinophilia, but total IgE was not high. Fluticasone 0.005% ointment, pimecrolimus 1%, zinc oxide 20%, and bland skin care led to improvement. He remains on tacrolimus (0.2 mg/kg/d, adjusted to goal serum trough 8–10 ng/mL) and mycophenolate mofetil

(20 mg/kg/d), with intermittent fluticasone and calcipotriol ointments marginally controlling his eczema over 18 months. Systemic tacrolimus has not been adjusted or discontinued because the patient's family and cardiologist feel the cardioprotective benefits of continuing his antirejection regimen outweigh the burden of cutaneous disease.

3 | CASE REPORTS SUMMARY

We present three cases of paradoxical eczema that developed in boys with iatrogenic immunocompromise after cardiac transplantation in

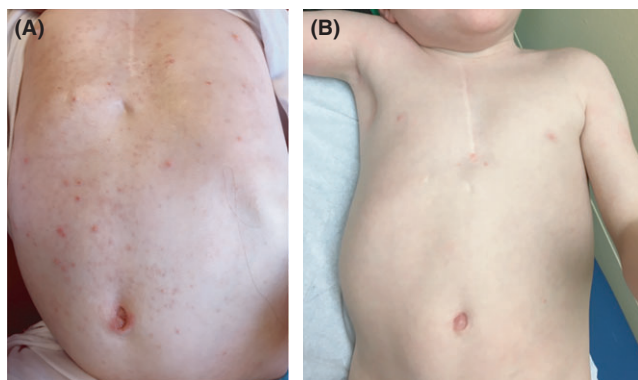


FIGURE 1 Trunk. (A) Age 3 years taking tacrolimus up to 0.14 mg/kg/d. (B) Age 4 years after tacrolimus reduction to 0.07 mg/kg/d

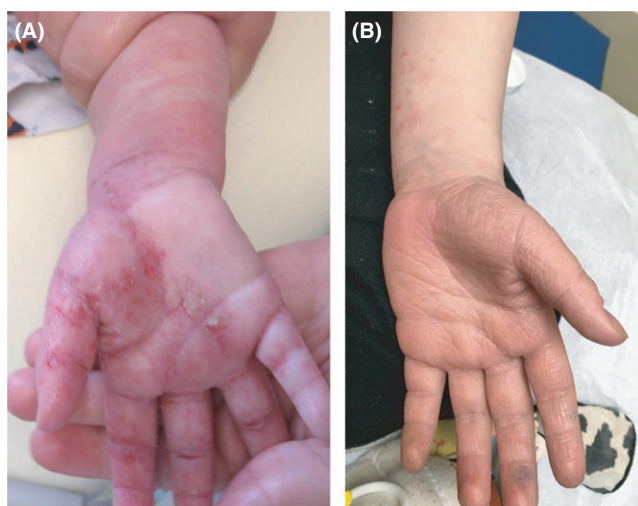


FIGURE 2 Hand and forearm. (A) Age 3 years taking tacrolimus up to 0.14 mg/kg/d. (B) Age 4 years after tacrolimus reduction to 0.07 mg/kg/d

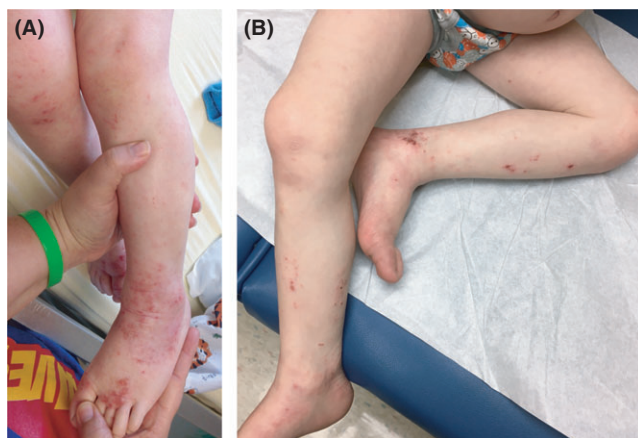


FIGURE 3 Leg. (A) Age 3 years taking tacrolimus up to 0.14 mg/kg/d. (B) Age 4 years after tacrolimus reduction to 0.07 mg/kg/d

infancy. They all had features indicative of partial DGS-VCFS, suggesting additional primary immune deficiency, but genetic testing (FISH) was negative for known mutations. The average duration of

immunosuppressant therapy before onset of eczema was 17.3 months (range 2–48 months). None of the patients had a prior personal or family history of atopy or psoriasis. Skin involvement was generalized. Two patients had a possible microbial trigger, with GAS or *S. aureus* colonization or both, and underwent tonsillectomy and adenoidectomy for recurrent extracutaneous infection. Skin care regimens were optimized with topical corticosteroids, topical calcineurin inhibitors, and antimicrobial agents, with some improvement. One patient required multiple hospitalizations for infection-triggered flares that did not respond to a trial of IVIG. Ultimately, oral tacrolimus dose reduction or withdrawal resulted in significant improvement in two patients. The third patient, who remains on oral tacrolimus, continues to have marginal control on topical therapy.

4 | DISCUSSION

Paradoxical psoriasis is a well-recognized adverse effect of TNF inhibitors given for inflammatory bowel or rheumatologic disease.¹ The paradoxical aspect refers to new-onset or worsening psoriasis in patients undergoing a treatment known to effectively treat this skin disease. Other patients taking TNF inhibitors for management of psoriasis experience disease worsening, including new plaques in previously uninvolved areas or a change in the morphology of the skin eruption.⁷ We describe an analogous paradoxical eczema in patients treated with systemic tacrolimus, a drug that is applied topically as the standard of care for eczema.⁸ A few reports have documented new-onset atopic-like dermatitis in children receiving systemic tacrolimus after solid organ transplantation.^{4,5,9,10} Our work adds three boys with iatrogenic and possibly primary immunodeficiency who were undergoing tacrolimus maintenance therapy after cardiac transplantation and presented with eczematous dermatitis.

Treatment for paradoxical eczema has not been defined. The refractory nature of eczematous skin disease in these patients prompted initial surveillance for potential confounding factors including microbial colonization, primary immunodeficiency, and atopy.¹¹ Bland skin care, topical corticosteroid and corticosteroid-sparing agents, antimicrobial prophylaxis, and allergen avoidance were mainstays of treatment. IVIG, which can be used to treat severe dermatitis^{12,13} as well as graft rejection,^{14,15} was discontinued in one patient because of concern about graft rejection, which is infrequently reported.¹⁶

Systemic tacrolimus withdrawal was followed by skin clearance in one patient, and a second patient improved after dose reduction. Prior reports document similar improvement in atopic disease after oral tacrolimus dose reduction or a change in therapy, including 12 pediatric liver recipients with a history of recurrent food-triggered angioedema or anaphylaxis whose tolerance,¹⁷ a 3-year-old heart recipient whose widespread eczema resolved,⁴ and an adult with type 1 diabetes who developed severe dermatitis after islet transplantation cleared.¹⁸ A theoretical risk of transplant rejection exists with discontinuation or dose reduction in immunosuppressant therapy for improvement of skin disease, although graft function remained stable in reports published to date.^{17,18}

Refractory eczema has been reported in transplant recipients undergoing a variety of antirejection regimens, including tacrolimus monotherapy and combination therapy with sirolimus, mycophenolate mofetil, and prednisone alone or in combination.^{4,9,17,18} Our patients developed eczema after transitioning to maintenance regimens including tacrolimus with or without mycophenolate mofetil or azathioprine. Dosing of antirejection therapy was within published norms and was adjusted to maintain therapeutic serum levels,¹⁹ favoring an association between eczema and systemic tacrolimus over an association with other antirejection drugs.

The development of paradoxical eczema in iatrogenically immunosuppressed patients may be related to skewed immune homeostasis and cutaneous dysbiosis. Systemic tacrolimus selectively inhibits cytokine transcription, steering the immune response toward Th2 differentiation, eosinophilia, and high IgE.^{2,20} All of our patients had eosinophilia while taking oral tacrolimus, and two of three had high total IgE (Table 2). One of our patients developed food allergies concomitant with worsening skin disease, similar to prior reports.⁹

Although there was no personal or family history of atopy in our patients or those previously reported,^{4,5} iatrogenic immunosuppression may unmask a predisposition towards atopy. In paradoxical psoriasis, genetic studies have identified variations in immune signaling pathways that might predispose susceptible individuals.^{1,21-23} In our patients, congenital cardiac anomalies and other somatic features suggestive of DGS-VCFS are suggestive of underlying primary immune dysregulation and atopic bias. Negative FISH does not exclude this as a contributing factor. Age at transplantation and immune maturation may also play a role in the disposition to eczematous dermatitis in individuals taking systemic tacrolimus. The average age of cardiac transplantation in our patients is among the youngest reported; older children taking systemic tacrolimus may be less likely to develop atopic disease.^{9,10}

In summary, we present three iatrogenically immunocompromised pediatric heart recipients taking systemic tacrolimus who developed paradoxical eczema. Despite negative FISH, DGS-VCFS was suspected on the basis of congenital cardiac disease requiring transplantation, developmental delay, and recurrent infection, although atopic dermatitis has been described in patients without these features taking maintenance tacrolimus after renal and hepatic transplantation. There are no pathognomonic clinical features or biomarkers that can differentiate atopic dermatitis from a medication-related adverse effect or immunodeficiency dermatitis. Skin biopsy can help exclude graft-versus-host disease and should be considered in patients with suggestive signs or symptoms (eg, sunburn-like changes, blisters, persistent abdominal pain, nausea, diarrhea, transaminitis). Clinicians who manage children taking antirejection medications after solid organ transplantation should be aware of this potential drug-associated adverse effect. Management of this condition can be challenging and may require coordinated multidisciplinary care. Surveillance for microbial triggers may provide insight during disease flares. Allergen avoidance, antimicrobial therapy, and topical corticosteroid and corticosteroid-sparing agents should be mainstays of therapy, with a goal of barrier restoration. Discontinuation or dose titration of tacrolimus and

initiation of alternative systemic immunosuppressant therapy may lead to skin clearance, but patients should be monitored closely for evidence of transplant rejection. Monitoring T-cell functional activity via standardized laboratory assays may provide one means of determining the dose of systemic antirejection therapy that effectively balances transplant tolerance with minimal cutaneous adverse effects. Such a strategy warrants more investigation.

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