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Atypical Acute Rejection After Hand Transplantation

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Skin rejection after hand transplantation is characterized by a maculopapular erythematous rash that may be diffuse, patchy or focal, and distributed over forearms and dorsum of the hands. This 'classical' pattern of rejection usually spares the skin of the palm and does not affect the nails. Herein, we report the experience on four cases presenting with an 'atypical' pattern of rejection that is novel in involving the palmar skin and the nails. All patients were young and exposed to repetitive and persistent mechanical stress of the palm. Characteristic features of rejection included a desquamative rash associated with dry skin, red papules, scaling and lichenification localized to the palm. Skin lesions were associated with nail dystrophy, degeneration, deformation or loss. Histology of the skin and nail bed revealed a lymphocytic infiltrate with predominance of T cells (CD3+, CD4+ and CD8+), with small numbers of B cells (CD20+ and CD79a+) and a low number of Forkhead transcription factor 3 (FOXP3)-positive cells in one patient. The lesions persisted over weeks to months, responded poorly to steroid treatment and were managed with antithymocyte globulin (ATG; Thymoglobulin, Genzyme, Cambridge, MA), alemtuzumab and/or intensified maintenance immunosuppression.

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Key words: Composite tissue transplantation, hand transplantation, nail, rejection, skin

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Introduction

The world experience in human hand transplantation to date includes 37 transplants performed in 27 recipients (www.handregistry.com). In that experience, the number of acute rejection episodes during the first year has been high when compared to more recent reports in organ transplantation. Furthermore, steroid-resistant rejections were frequently observed, and required treatment with antithymocyte globulin (ATG; Thymoglobulin, Genzyme, Cambridge, MA), basiliximab or alemtuzumab (1,2,4). Reports indicate that the majority of patients demonstrated at least one episode of acute rejection in the first year, and that skin was the primary target of the immune response (1–7). Repeated episodes were observed in some patients beyond the first year after transplantation (4–6). The high frequency and severity of acute rejection in hand transplantation has been attributed to the high immunogenicity of the skin, which forms a major component of the graft. The high antigenicity of the skin can, in part, be related to the high proportion of potent antigen-presenting cells (Langerhans cells) and keratinocytes that express major histocompatibility complex (MHC) I constitutively, and MHC II, intercellular adhesion molecule 1 (ICAM)-I and proinflammatory cytokines upon stimulation (8–11). Also, viral infections, in particular cytomegalovirus (CMV), have been postulated to trigger the episodes (12). It has been postulated that the higher incidence of acute rejection reported in hand transplants is due to the ability to visually detect rejection (resulting in an increased positive prevalence). Accessibility of the skin component of a hand allograft enables biopsies to be taken routinely, and whenever clinical suspicion warrants histopathologic confirmation. Thus, visual monitoring allows for diagnosis of conditions in hand transplants that may often be missed in organ transplants.

Acute rejection has been characterized as a maculopapular erythematous skin rash that may be diffuse, patchy or focal, with or without burning pain. The lesions, what we refer to as the 'classic' type of rejection in hand transplantation, affect the dorsal and volar aspects of the forearm

and wrist and the dorsum of the hand in some cases. The palm of the hand and the nails, however, are spared.

Herein, we report the combined experience with four hand transplant recipients (from Belgium, Italy, Austria and the United States) with specific reference to an 'atypical' presentation of rejection that differs from the 'classically' established description of the phenomenon in terms of novel involvement of palmar skin, the appearance of skin lesions, associated nail changes, as well as the response to treatment.

Patients

Four patients underwent unilateral (n = 3) or bilateral (n = 1) hand transplantation. All transplants were performed with Institutional Review Board or Human Studies Committee approval, and in accordance with Independent Ethics Committee regulations. The level of amputation was the mid (n = 2) or distal (n = 2) forearm. All patients were comparably young (22–36 years), and three of them had a good (3/3) HLA match with the donor, whereas one patient had a full mismatch. There was no CMV mismatch in any of the cases, but two patients were positive for CMV prior to transplantation. Induction therapy included basiliximab (#2 and #4) in two patients and ATG (#1) or alemtuzumab (#3) in the other two patients. For maintenance, all patients received tacrolimus, mycophenolate mofetil (MMF) and steroids. In one patient (#4), tacrolimus was replaced by rapamycin due to drug-induced hyperglycemia at 3 weeks. Graft monitoring was performed by visual inspection and skin biopsy, whenever clinically indicated. Patient information is also summarized in Table 1.

Methods

Histology and immunohistochemistry

Clinical and histopathologic assessment of rejection was performed according to established criteria (1,2,4–7,13). Biopsy samples were routinely fixed in formalin, embedded in paraffin, stained with hematoxylin and eosin (H&E) and blind examined by a pathologist. Acute rejection was graded as per two classifications that have been published earlier (6,13). Skin biopsy samples were taken routinely during the early period after transplantation and upon clinical evidence of rejection at later time points. A nail bed biopsy was performed upon nail rejection. Tissues other than the skin were examined in one patient following collection during a scar revision. Antibodies against CD3, CD4, CD8, CD20, CD68, CD79a and Forkhead transcription factor 3 (FOXP3) were used for immunohistochemical investigation of any cellular infiltrate. C4d staining was performed to investigate for antibody-mediated rejection in some patients. Biopsies have been taken after treatment of rejection in two cases. In the other two cases, the rejection had resolved clinically, but no biopsy has been performed.

Functional assessment

Functional outcomes were scored in patients by the Hand Transplantation Score System (HTSS) developed by the International Registry for Hand and Composite Tissue Transplantation (IRHCTT) (14). A total of six functional areas were scored (a total of 100 points) in each patient (10): appearance (15 points), sensibility (20 points), movement (20 points), psychological and social acceptance (15 points), daily activities and work status (15 points) and patient satisfaction and general well being (15 points). A total result of 81–100 points is graded as an excellent outcome, 61–80 as good, 31–60 as fair and 0–30 as poor.

Results

Clinical presentation of atypical rejection

The lesions observed in all four cases were characterized by an erythematous rash of the palm, together with soft

Table 1: Patient demographics

	Patient #1 (Belgium)	Patient #2 (Italy)	Patient #3 (Austria)	Patient #4 (USA)
Amputation	Traumatic	Traumatic	Traumatic	Traumatic
Gender of recipient	Male	Male	Male	Male
Occupation	Butcher	Farmer	Student	Gutter-installer
Age at transplant	22 years	32 years	23 years	36 years
Duration after amputation	20 months	48 months	60 months	60 months
Prosthesis used	Myoelectric	Cosmetic, mechanical	None	Cable-hook
Transplant	Unilateral	Unilateral	Bilateral	Unilateral
Date transplanted	June 2002	October 2001	May 2006	February 2001
Ischemia time	6 h	11.5 h	3 h	3 h
HLA mismatches	3/6	3/6	3/6	6/6
Crossmatch (pretransplant)	Negative	Negative	Negative	Negative
Donor CMV sero-status	Negative	Positive	Positive	Negative
Recipient CMV sero-status	Negative	Positive	Positive	Negative
Induction regimen	Antithymocyte globulin	Basiliximab	Alemtuzumab	Basiliximab
Maintenance regimen	Tacrolimus + MMF + steroids	Tacrolimus + MMF + steroids	Tacrolimus + MMF + steroids	Rapamycin + MMF + steroids
Follow-up	57 months	65 months	9 months	73 months

All patients were young, and three had a good HLA match. Induction therapy was given to all patients followed by maintenance immunosuppression with tacrolimus (n = 3) or rapamycine (n = 1), MMF and steroids.

Table 2: Summary of the clinical courses and the features of rejection in four patients

Patient	Signs and symptoms	Histopathology and immunohistochemistry	Clinical course and outcome
#1	Diffuse rash on the palm, progressive dryness and skin scaling, finger swelling, onychomadesis, nail loss and burning pain.	Grade 3 rejection with T-cell (CD3+) and B-cell (CD20+, CD79a+) infiltration. Hyperkeratinization, spongiosis, prominent lymphocytic infiltrate in superficial dermis, erosion of the basal epidermis and cytoid bodies. FOXP3+ cells in the chronic inflammatory cell infiltrate	Thinning of nail plate, nail regrowth at 50 months and spontaneous resolution of skin lesions following UV exposure. Normal motor and sensory function.
#2	Patchy erythema, palmar rash, edema, onychomadesis, nail loss, diffuse hair loss, skin scaling and thickening.	Grades 1–3 rejection, perivascular lymphocytic infiltrates in dermis, no signs of acute rejection in epidermis. Extensor tendon, bone and vessels appeared normal. No immunohistochemistry performed.	Regrowth of dystrophic and soft nails, finger stiffness and reduced function but normal sensation.
#3	Palmar rash and scaling. Transverse leukonychia in nails on both hands.	Diffuse lymphocytic infiltrate in upper dermis, interphase reaction, single cytoid bodies along basal membrane, cellular infiltrate predominantly comprised of CD4+ T cells and to a lesser extent CD8+ T cells and CD68+ macrophages, acral skin interface dermatitis, cytoid bodies and spongiosis.	Continued nail growth (soft, thin) following treatment of acute rejection, persistent dryness of palmar skin and persistence of minimal perivascular cellular infiltrate preceding normalization of skin histology.
#4	Diffuse maculopapular palmar rash, ridging and transverse leukonychia of nails.	Lymphocytic and eosinophilic infiltrate around the vessels with frank epidermal, stromal and adnexal involvements and mild spongiosis, little or no staining with FOXP3+, CD20+, CD79a+ and CD68+ cells, but significant perivascular infiltrates staining for T-cell markers (CD3, CD4, CD8 [lesser than CD4] and CD25).	Slow but complete resolution of nail and palmar lesions without specific intervention and persistent cellular infiltrates that correspond to a histologic grades 0–1 rejection.

The appearance, histology and immunohistochemistry of 'atypical' rejection are reflected by a desquamative rash associated with dry skin and scaling at the palm. Nails were disfigured in two patients, and lost in the other two cases. Histology revealed a lymphocytic infiltrate (T cells positive for CD3, CD4, CD8 and a small number of B cells, and an increasing number of FOXP3+ cells). The clinical courses and respective treatment are summarized for each patient.

tissue swelling of the fingers (Figure 1A). Erythematous lesions that affected the forearm and/or the dorsum of the hand resolved spontaneously or by treatment in patients, whereas those on the palm were resistant to conventional drug intervention. Dryness, scaling and thickening of palmar skin were associated with characteristic nail changes (Figure 1B). Such atypical manifestations of rejection strikingly resembled psoriasis. Loss of hair on the allograft was observed in one patient. Early nail changes in two patients included proximal separation of the nail from the nail bed, leading to complete loss of the nail and the nail plate (Figure 1C; onychomadesis). In these cases, nail regrowth occurred, but nails remained dystrophic, soft and brittle during the entire observation period. The nail plate was thin, but was reforming. In two patients, dystrophic changes like leukonychia were noted that corresponded in timing of onset with rejection episodes (Figure 1D). Nail growth continued following successful treatment of acute rejection, but the growing nails differed in color, thickness and texture. Motor and sensory functions of the hand were affected by rejection in one case; however, radiographs of hand, wrist and forearm remained normal. Motor function and discriminative sensation were preserved in all other patients. One patient complained of an intense burning pain resembling sunburn during rejection. In most cases, all lesions resolved completely. However, one patient continued to have dryness of the palmar skin and finger stiffness.

Histopathologic and immunohistochemical findings

Biopsies of palmar skin taken during the course of 'atypical rejection' showed a variable degree of lymphocytic infiltrate that commenced in the perivascular and perineural areas of the dermis (acute rejection grade 1, Figure 2A), and progressed into the superficial dermis with erosion of basal epidermis in some cases (Figure 2B). Skin samples revealed epidermal 'hyperkeratinization', with evidence of spongiosis and appearance of cytoid bodies (Figure 2C; eosinophilic, round, homogeneous structures seen in basal epidermis or upper dermis. They form through degeneration of epidermal cells like keratinocytes, and are most commonly seen in lichenoid tissue reactions). A nail bed biopsy showed a lymphocytic infiltrate similar to what has been observed in the palmar skin. With treatment, the histologic picture slowly altered to a persistent keratinization with reduced lymphocytic and macrophage infiltrates in the epidermis and dermis. The cellular infiltrate resolved entirely in one case, and regressed to a very mild perivascular lymphozytic infiltrate in another case. Immunohistochemistry revealed a predominance of T cells (CD3+, Figure 2E), together with a small number of B cells (CD20+ and CD79a+). The T-cell infiltrate predominantly comprised CD4+ T cells and, to a lesser extent, CD8+ T (Figure 2F) cells and CD68+ (Figure 2G) macrophages. When immunostaining was performed, a minority of cells were found to express FOXP3+ (Figure 2H). In two patients,

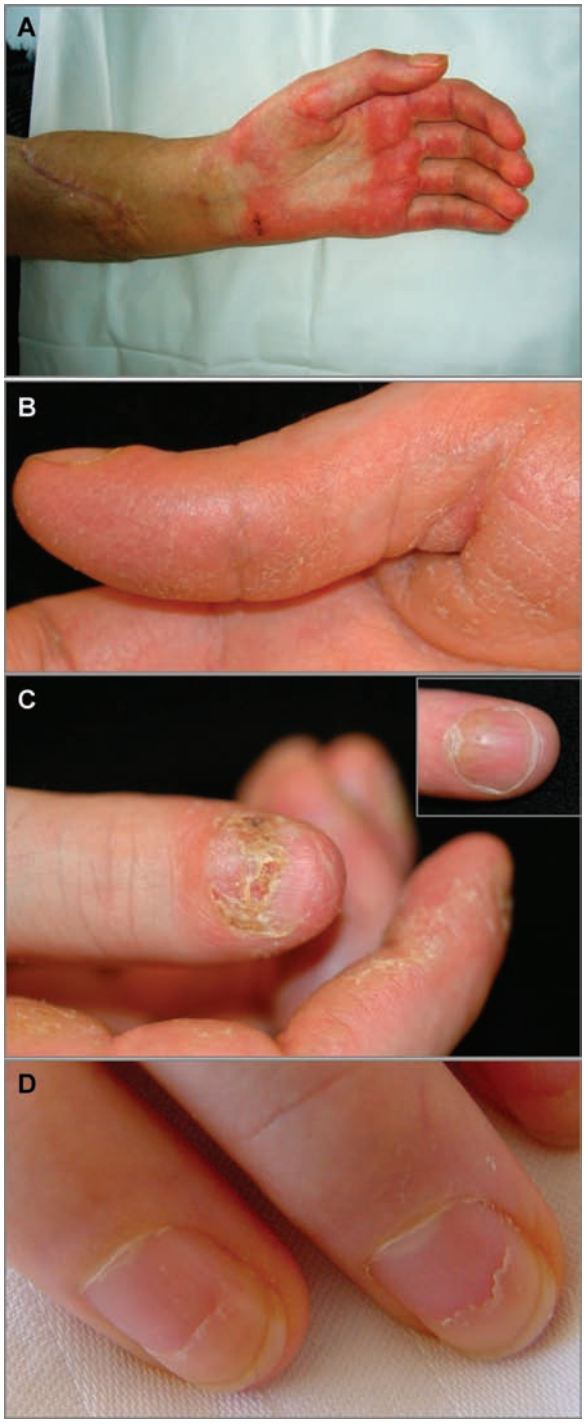

Figure 1: Appearance of atypical rejection. The lesions are characterized by an erythematous rash of the palm and finger swelling (A). Upon progression, dryness and scaling of the palmar skin was observed (B) and associated with nail lesions (insert) or nail loss (C). Nail growth continued following treatment of rejection, however, nails were thinner and weaker and differed in color. Leukonychia corresponded in time of onset with rejection episodes (D).

the proportion of FOXP3-positive cells increased over time. Samples were negative for C4d in all cases analyzed (data not shown).

Case reports

Patient #1 (Brussels, Belgium): The clinical course of this patient until 37 months after transplantation was published previously (3). At 43 months, following a period of questionable medication compliance, he presented with clinical rejection (Figures 3A and 3B) that was biopsy confirmed (grade 3, Figures 3C–3H). Palmar involvement with early evidence of onychomadesis was observed. The patient was treated with methylprednisolone, 500 mg/day i.v. for 3 days. Maintenance immunosuppression was increased (MMF from 1 g/day to 2 g/day and prednisone from 4 mg/day to 8 mg/day). Topical treatment with corticosteroid (diprosone, Schering Plough, Kenilworth, NJ) and tacrolimus ointment (Protopic, Astellas, Munich, Germany) was instituted. Erythema diminished on both the dorsal and volar aspects of the forearm, but persisted on the palm. The palmar skin became progressively dry and scaly (Figure 3I), and this culminated in loss of all nails (Figure 3J). Biopsies of the palm revealed persistent keratinization with lymphocytic and macrophage infiltrates in the epidermis and dermis (Figures 3G and 3H). When compared with earlier time points, immunostaining confirmed the presence of increased number of FOXP3+ cells (Figures 3M and 3N). Nail regrowth was noted at 50 months (7 months after onset of rejection). At 53 months, MMF was temporarily discontinued due to protracted diarrhea. This led to resurgence of rejection in forearm and palm, as seen at 43 months. Methylprednisolone, 500 mg/day was given for 3 days. Tacrolimus dose was increased from 2 mg/day to 3 mg/day bid (trough level after dose increase: 12.7 ng/mL), methylprednisolone dose was increased from 6 mg/day to 16 mg/day, and MMF was restarted at 500 mg tid. All skin lesions spontaneously resolved a month later, coincident with a trip to the Caribbean, with no relapse or recurrence of rejection (current drug trough levels: MMF [2.4 μg/mL] and tacrolimus [11.6 ng/mL]). Hand function at 5 years was 88.5 of 100 points.

Patient #2 (Monza, Italy): Acute rejection grade 1 was observed on both the dorsal and volar surfaces of the distal forearm (palm unaffected) at 3 months after transplantation, and was treated with steroids (500 mg/day i.v. for 2 days, and 250 and 125 mg i.v. for the two consecutive days). At 27 months, a second acute rejection episode (grade 3, lymphocytic infiltration of dermis and adnexae with spongiosis) was observed (Figures 4A and 4B), which had been progressing for 3 weeks before reported by the patient. Hand and forearm edemas, diffuse or patchy erythema and dryness/scaling of palmar skin were noted along with loss of nails and hair in the allograft. Erythema resolved with corticosteroids (500 mg/day for 2 days, 250 mg i.v. for 1 day and 125 mg i.v. for 1 day) and topical tacrolimus ointment for 14 days, but scaling of skin

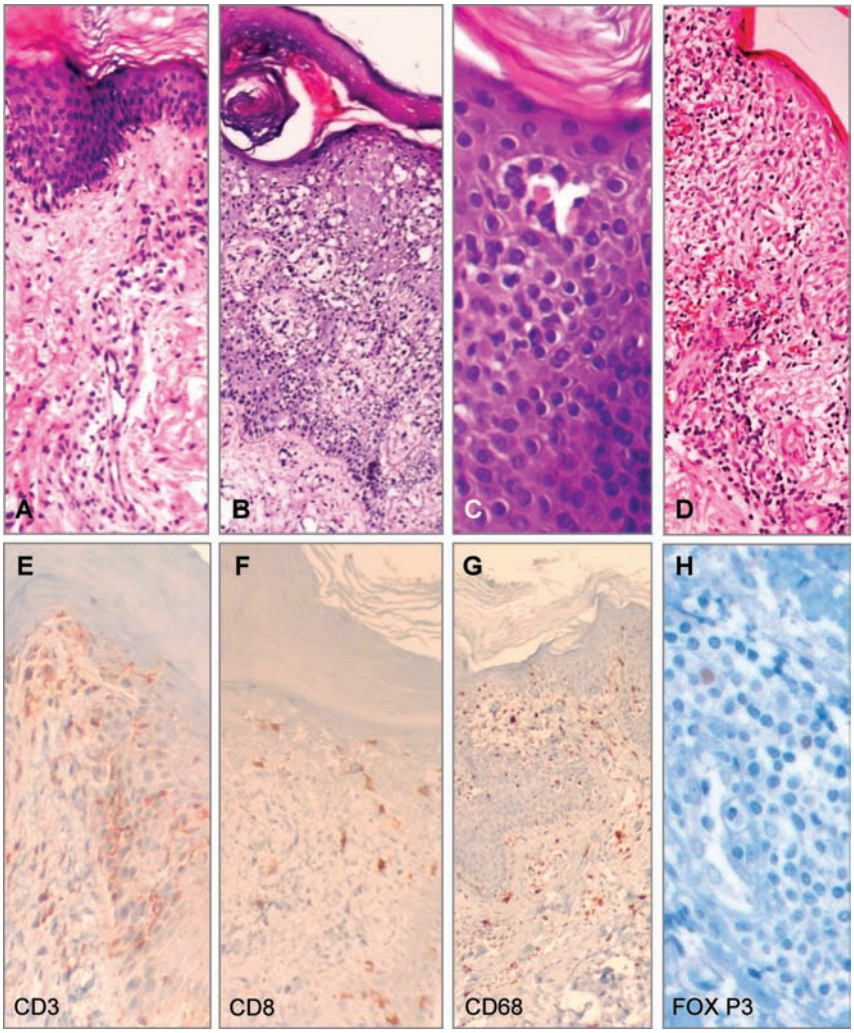

Figure 2: Histology and immunohistochemical analysis of rejection. A lymphocytic infiltrate was seen in all biopsies and progressed from the perivascular and perineural areas of the dermis (A) toward the superficial dermis and the epidermis (B). Epidermal 'hyperkeratinisation' and spongiosis, together with cytoid bodies, were observed (C). A dense cellular infiltrate confirmed rejection in nail bed biopsies taken at that time point. The majority of infiltrating cells are CD3+ T cells (E). Cytotoxic T- cells (F) are present in a small number. CD68+ macrophages (G) are found in dermis and epidermis. A minority of cells in the infiltrate stained positive for FOXP3 (H), but the proportion of these cells increase over time in two patients.

(Figures 4C and 4D), palmar thickening and hand edema persisted. Nail regrow occurred after 1 month, but they remained dystrophic for over 8 months, and soft thereafter. Finger stiffness was noted. This subsided with physiotherapy, but recurred upon discontinuation of therapy. Vascular patency was confirmed in both radial and ulnar arteries by arteriography. Sensation remained unaffected. Five years after transplantation, hand function was 69 of 100 as evaluated by the HTSS (10). This is lower when compared to that at 24 months (82/100). Nails have now regrown, and the patient has returned to professional duties.

Patient #3 (Innsbruck, Austria): The patient was free of clinical signs of rejection until day 51. Papular erythema over the dorsal right hand (Figure 5A) progressed over both forearms, with sparing of fingers and the palm (Figure 5B). Skin biopsies showed acute rejection (grade 2) that was successfully treated with solumedrol (methylprednisolone) i.v. 500 mg/day for 3 days. On day 60, a diffuse rash on the palmar aspect of both hands and finger joints was observed (Figures 5C and 5D). Histology revealed grade 3 acute rejection (Figures 5E–5H). Solumedrol bolus treatment together with topical tacrolimus ointment and clobetasol cream did not have any effect, and rebiopsy revealed progressive rejection. Alemtuzumab was administered at a dose of 20 mg with simultaneous stoppage of MMF, topical steroid and tacrolimus ointment. Following alemtuzumab treatment, lymphocyte counts dropped to 0–1%. Scaly lesions developed in the palm (Figure 5I) and spontaneously disappeared after 4 weeks (Figure 5J). Bilateral leukonychia and nail dystrophy was noted and corresponded in time with the onset of rejection (on day 60). Newly growing nails differed in color, thickness and texture (Figure 5K). A skin biopsy taken after restoration of normal skin appearance showed normal skin histology (Figure 5L). Hand function at 1 year after transplantation is 64 of 100 and 65.5 of 100 points for the left and right sides, respectively.

Patient #4 (Louisville, KY): Four 'classical' acute rejections were observed early on postoperative days 10 (grade 1), 21 (grade 2), 50 (grade 2) and 77 (grade 2). The first rejection was treated with methylprednisolone

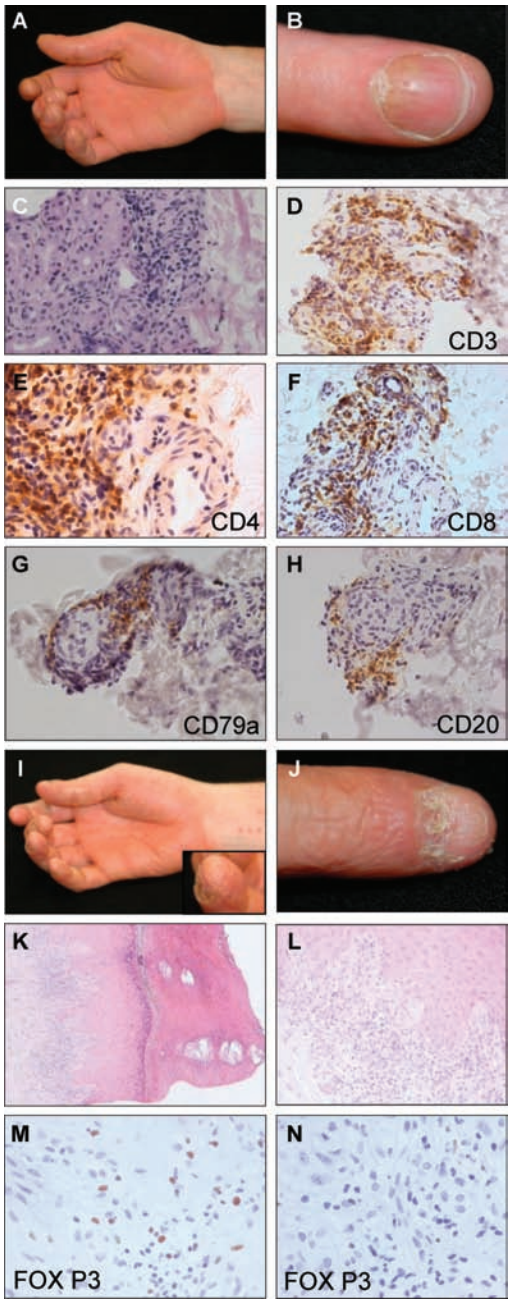

Figure 3: Patient #1. An erythema, swelling and scaling, together with first signs of onychomadesis, were observed at 43 months (A, B). The infiltrate was predominant in the epidermis and sweat glands (C) and comprised T cell (CD3) and B cells (CD79a, CD20) (D–H). The majority of infiltrating T cells stained positive for CD4 (E). CD8+ cells comprised a smaller proportion of the infiltrate (F). In response to treatment, the palm skin became dry and scaly (I). Onychomadesis progressed and resulted in loss of all nails (J). The lymphocytic infiltrate spread over dermis and interphase between dermis and epidermis (K, L). FOXP3$^+$ cells were found as part of the infiltrate (N). The number of FOXP3-positive cells was increased when compared to the biopsy taken 5 months earlier (M).

and topical tacrolimus (Protopic, Astellas, Deerfield, IL) and clobetasol, the second rejection was treated with methylprednisolone and an increase of oral prednisone to 100 mg/day for 4 days, the third rejection was treated with rabbit ATG and the fourth rejection was treated with topical tacrolimus and clobetasol. At 3 months, biopsies taken from a rejection at the forearm (Figure 6A) and palmar rash (Figure 6B) confirmed grade 2 acute rejection (Figure 6C) and characteristic dystrophic nail changes (Figure 4E). Rejection was treated with methylprednisolone i.v. (100 mg initially followed by 500 mg) over a period of 3 days. Although the erythema at the forearm responded, the palmar erythema and nail changes persisted. Topical tacrolimus and clobetasol treatment was continued, but showed minimal effect. At day 127, persistent acute rejection (grade 2) was diagnosed with characteristic immunohistochemistry changes (Figures 6D–6H). The forearm and wrist rashes relapsed on the dorsal and volar aspects, and the palmar rash intensified. Nail changes persisted. The dorsal and volar forearms and wrist rash cleared with the use of topical steroids, but the palmar rash and nail changes persisted (Figures 6I and 6J). A biopsy shows normal histology of the epidermis, but a mild perivascular lymphocytic infiltrate in the dermis (Figures 6K and 6L). The functional outcome as evaluated according to the HTSS is 50 of 100 at 6 years.

Discussion

Outcomes data from hand transplants, performed over the past 9 years around the world, confirm that acute rejection of the skin classically involves and is restricted to the dorsal and volar aspects of the forearm and wrist (1,2,4–7,13). Such involvement can be patchy and localized or diffuse and uniform in nature. The groups contributing to this article have altogether observed a total number of 34 rejection episodes in the patients transplanted in the respective centers. In contrast and in addition to classical rejection, some patients (as discussed here) experienced an atypical form of rejection that differed substantially in appearance, distribution, progression, character and response to treatment from all other rejections observed to date. Notably and as never reported earlier, these patients demonstrated a desquamative palmar rash associated with nail dystrophy, degeneration or damage. Thus, the rejection was not only 'atypical' but 'novel' in the heterogenic pattern of involvement of palmar skin and appendages like nails. The involvement of the nail bed/matrix by rejection leads to weakening/thinning of nail plate, followed by loosening of the nail from its bed. A biopsy of the nail bed confirmed presence of a dense lymphocytic infiltrate being the histomorphologic substrate. Although steroid resistance has also been observed in other rejections, this pattern of rejection seems to be associated with a consistent resistance to steroid treatment.

In the context of involvement of the palm, it is interesting to note that an anamnestic feature common to all four

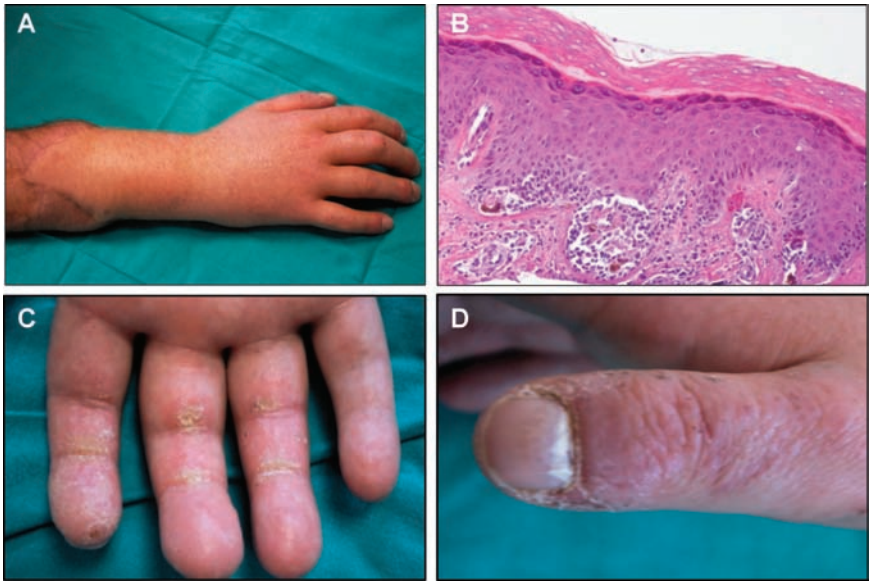

Figure 4: Patient #2. A third acute rejection (grade 3) was observed at 27 months (A, B) in patient #2. At this time, all nails and a large proportion of the hair on the transplant were lost. Biopsy confirmed acute rejection (grade 3). Scaling of the skin persisted even after treatment of rejection (C, D).

patients was some form of mechanical stress to the palm. The evolutionary advantage that is inherent to palmar skin relates to its thickness. The thicker skin of the palm protects the hand from trauma, and sustains the repeated stresses due to daily activity. Although all patients were relatively young and on similar immunosuppressive regimens, the fact that all of them were either involved in professions involving manual use of their hands in tasks or exposed to intense physical hand therapy that resulted in a degree of mechanical stress might be of relevance. Repetitive and significant mechanical stress could not only initiate, but also sustain an inflammatory and immune response in the skin of the palm. A neutrophil-mediated induction and acceleration of acute rejection has been described previously, and might also be a relevant mechanism in this context (15).

Histology of skin revealed parakeratosis, spongiosis, interface dermatitis and appearance of cytoid bodies, together with an infiltrate comprising lymphocytes and macrophages in the dermis and epidermis. Although similar to previously described skin rejection with regard to composition of cellular infiltrate, the histologic appearance differed from classical rejection in terms of prominence of parakeratosis and spongiosis. The definitive histologic classification of this type of rejection, however, warrants a larger number of cases and a systematic approach to analyze the characteristics of progression of rejection, ideally together with an analysis of rejection of the palm in a suitable animal model.

It has been described in the organ transplant literature that immunosuppressive agents can induce skin lesions that can mimic the appearance of atopic dermatitis or psoriasis. Hand transplant recipients around the world are on similar drug regimens as used widely in solid organs, and could succumb to similar cutaneous adverse effects secondary to these drugs. Psoriasis can be triggered by nonsteroidal anti-inflammatory drugs, diuretics, beta-blockers and prednisone (16). Although it may be problematic to make a definitive cause-and-effect link between administration of prednisone and development of the lesions, such an association seems unlikely, especially as the lesions resolved in all four patients despite ongoing prednisone therapy. Resolution of the palmar erythema and desquamation and improvement of nail lesions in all cases, though apparently 'spontaneous' in some cases, was probably caused by ongoing or increased immunosuppression.

Nail changes have also been shown to occur in organ transplant patients on immunosuppression (17). The use of rapamycin in renal transplant patients has been associated with transverse leukonychia, a feature seen in patient #4, who was incidentally on rapamycin (18). One case of MMF-associated onychomadesis was reported in a renal transplant patient on MMF, tacrolimus and prednisone. In this case, the nails regrew upon discontinuing MMF, but loosening occurred upon restarting MMF (19). All the patients in our study were treated with MMF. Although it is intriguing to consider a connection between the nail changes and rapamycin or MMF, such a link cannot be scientifically confirmed. Importantly, the lesions improved/resolved while the patients were on these drugs. Furthermore, nail changes reappeared after MMF was discontinued for diarrhea in patient #1, and improved after MMF was restarted at a later time point.

Desquamation of skin has been reported in graft-versus-host disease (GvHD). In this context, it is interesting to note that appearance and histology of the rejection described here resembles GvHD in a unique way. This observation further underlines the common belief that rejection and GvHD represent the responses of two counteractive

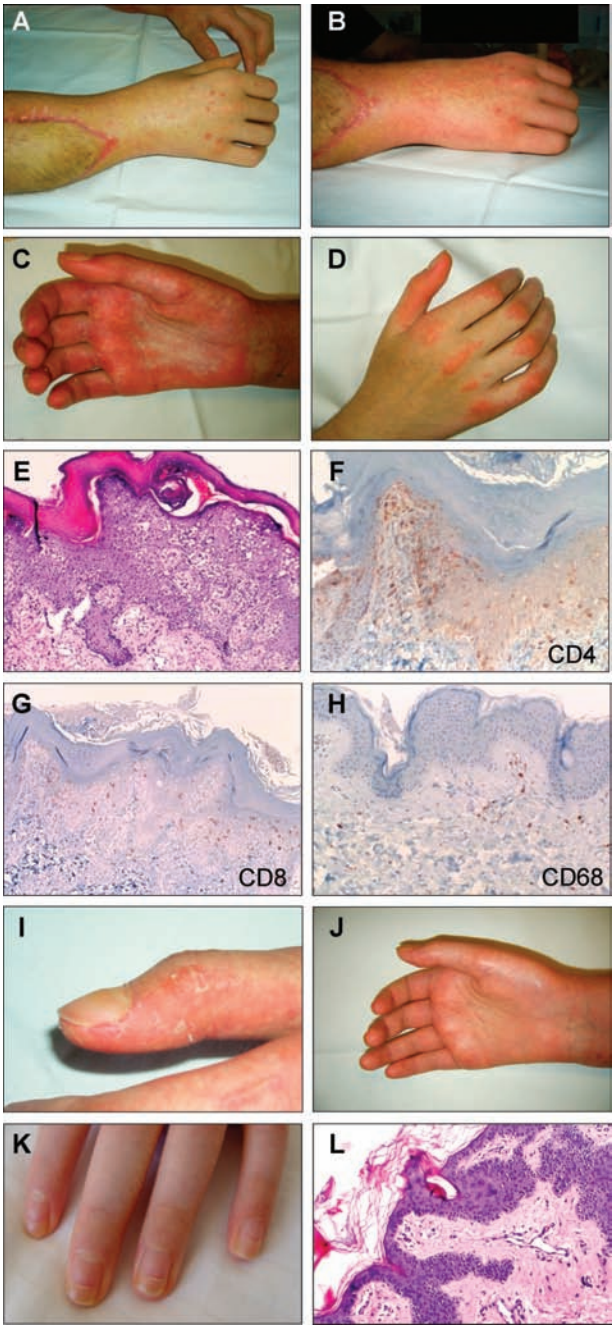

Figure 5: Patient #3. At day 51, erythematous papules were observed on the dorsal side of the hand (A). Erythema and papules spread over the entire graft, except for fingers and palm (B). Nine days later, a rash developed on the palm and the finger joints (C, D). A skin biopsy revealed acute rejection (grade 3) and an infiltrate comprising CD4+ and CD8+ T cells and CD68+ macrophages (E–H). Following treatment with alemtuzumab, scaly lesions were observed at the palm (I) before all skin lesions disappeared (J). Transverse leukonychia corresponded in time with the onset of rejection (K). Regrowing nails differed in color, thickness and texture. A biopsy taken after disappearance of skin lesions showed normal skin histology (L).

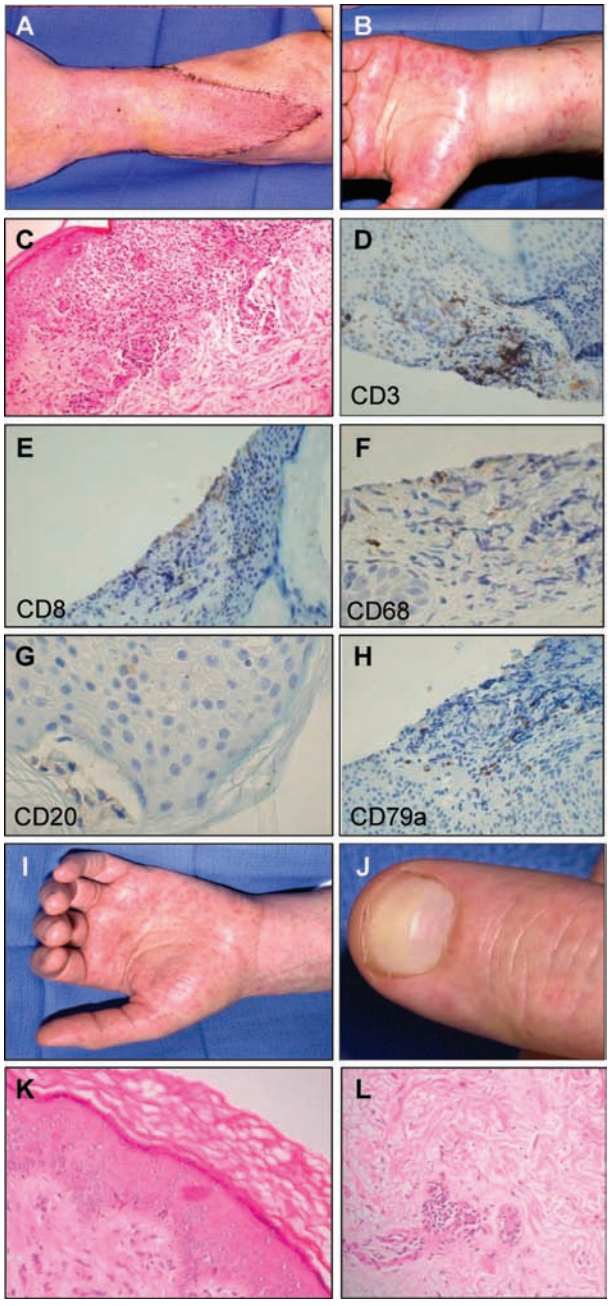

Figure 6: Patient #4. At 3 months, acute rejection with a diffuse and intense maculopapular rash on the forearm was noted (A) that progressed toward the palm (B). Biopsies showed a lymphocytic and eosinophilic infiltrate around the vessels with frank epidermal, stromal and adnexal involvements and mild spongiosis (C). The infiltrate comprised CD3+ T cells (D) cytotoxic T-cells (E), macrophages (F) and a small number of B cells (G) and precursor B cells (H). Clinical features of rejection of the palm diminished after antithymocyte globulin infusion, but some lesions persisted (I). The nails revealed transverse, spotty leukonychia, ridging and discoloration corresponding with time of rejection (J). Treatment resulted in normalization of histology, except for a persistent mild perivascular lymphocytic infiltrate (K, L).

but equally functional immune systems, one acting against the allograft (rejection) and the other one against the host (GvHD) (20).

Nail and palm lesions, similar to those described here, have been previously observed in response to medication noncompliance in the first patient who received a hand transplant in Lyon in 1998 (21). In these cases, however, lesions spread over the entire graft and were not restricted to palm and nails. Palmar skin remains dry in three patients, while it is normal in patient #4 (sweating has returned). Patient #4 continues to show minor but persistent perivascular lymphocytic infiltration. In this, as well as other recipients of hand transplants, a chronic lymphocytic infiltrate was found. However, rejection developed rapidly (within days), and resolved slowly but entirely in most cases. The classic features of chronic rejection, namely myointimal proliferation of allograft vessels and evidence of interstitial fibrosis, were not observed. Nevertheless, we consider finger stiffness observed in one patient to signify underlying fibrotic changes, and such a finding might predate or herald chronic rejection in human hand transplantation.

In summary, an atypical rejection, characterized by palmar involvement and nail changes, was observed in all patients reported here. The characteristics that distinguish such 'atypical' rejection from 'classical' acute rejection are primarily the palmar involvement and nail changes. To our knowledge, this novel type of rejection is distinct in all previously described forms of rejection, suggesting that the manifestations of rejection in composite tissue allotransplantation might be more heterogeneous than previously believed and associated with diverse clinical implications. Noncompliance increases the incidence, but rejection can also be observed despite appropriate immunosuppressive therapy. Careful monitoring of the graft for acute rejection by visual inspection is important and must be emphasized in all patients. Early reporting of rejection by patients based on self-evaluation and timely recognition of clinical findings is essential for appropriate and effective intervention.

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References

1. Lanzetta M, Petruzzo P, Margreiter R et al. The International Registry on Hand and Composite Tissue Transplantation. Transplantation 2005; 79: 1210–1214.
2. Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. N Engl J Med 2000; 343: 468–473.
3. Schuind F, Van Holder C, Mouraux D et al. The first Belgian hand transplantation – 37 month term results. J Hand Surg [Br] 2006; 31: 371–376.
4. Schneeberger S, Ninkovic M, Piza-Katzer H et al. Status 5 years after bilateral hand transplantation. Am J Transplant 2006; 6: 834–841.
5. Schneeberger S, Ninkovic M, Gabl M et al. First forearm transplantation: Outcome after 3 years. Am J Transplant 2007; 7: 1753–1762.
6. Schneeberger S, Kreczy A, Brandacher G, Steurer W, Margreiter R. Steroid- and ATG-resistant rejection after double forearm transplantation responds to Campath-1 H. Am J Transplant 2004; 4: 1372–1374.
7. Schuind F, Abramowicz D, Schneeberger S. Hand transplantation: The state-of-the-art. J Hand Surg [Br] 2007; 32: 2–17.
8. Sugita K, Kabashima K, Atarashi K, Shimauchi T, Kobayashi M, Tokura Y. Innate immunity mediated by epidermal keratinocytes promotes acquired immunity involving Langerhans cells and T cells in the skin. Clin Exp Immunol 2007; 147: 176–183.
9. Czernielewski JM, Bagot M. Class II MHC antigen expression by human keratinocytes results from lympho-epidermal interactions and gamma-interferon production. Clin Exp Immunol 1986; 66: 295–302.
10. Uchi H, Terao H, Koga T, Furue M. Cytokines and chemokines in the epidermis. J Dermatol Sci 2000; 24(Suppl 1): S29–S38.
11. Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: From clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. J Am Acad Dermatol 2002; 46: 228–241.
12. Schneeberger S, Lucchina S, Lanzetta M et al. Cytomegalovirus-related complications in human hand transplantation. Transplantation 2005; 80: 441–447.
13. Kanitakis J, Petruzzo P, Jullien D et al. Pathological score for the evaluation of allograft rejection in human hand (composite tissue) allotransplantation. Eur J Dermatol 2005; 15: 235–238.
14. Lanzetta M, Petruzzo P, Margreiter R et al. Second report of the International Registry of Hand and Composite Tissue Transplantation. Transplant Immunol 2007; 18: 1–6.
15. Morita K, Miura M, Paolone DR et al. Early chemokine cascades in murine cardiac grafts regulate T cell recruitment and progression of acute allograft rejection. J Immunol 2001; 167: 2979–2984.
16. Mrowietz U, Elder JT, Barker J. The importance of disease associations and concomitant therapy for the long-term management of psoriasis patients. Arch Dermatol Res 2006; 298: 309–319.
17. Saray Y, Seckin D, Gulec AT, Akgun S, Haberal M. Nail disorders in hemodialysis patients and renal transplant recipients: A case-control study. J Am Acad Dermatol 2004; 50: 197–202.
18. Mahe E, Morelon E, Lechaton S, Kreis H, De Prost Y, Bodemer C. Sirolimus-induced onychopathy in renal transplant recipients. Ann Dermatol Venereol 2006; 133: 531–535.
19. Rault R. Mycophenolate-associated onycholysis. Ann Intern Med 2000; 133: 921–922.
20. Marcos A, Lakkis F, Starzl TE. Tolerance for organ recipients: A clash of paradigms. Liver Transpl 2006; 12: 1448–1451.
21. Kanitakis J, Jullien D, Petruzzo P et al. Clinicopathologic features of graft rejection of the first human hand allograft. Transplantation 2003; 76: 688–693.