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ORIGINAL ARTICLE

Nail changes in upper extremity allotransplantation: onychomadesis as the presenting sign of allograft rejection – a retrospective study

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SUMMARY

Upper extremity allotransplantation (UEA) is the more common type of vascularized composite allotransplantation of which more than 80 patients have benefited worldwide. These allografts include – along with the skin – the nail unit, a specialized epithelial appendage which may be the target of graft rejection. We report an UEA recipient who developed, as an initial manifestation of graft rejection, onychomadesis, that is shedding of the nail plate starting from the proximal nail bed. On this occasion, we reviewed the nail changes we have observed in a series of eight patients with UEA who were grafted and followed in our hospital since 1998 (mean follow-up period of 9.75 years). We also reviewed the relevant literature reporting nail changes in UEA recipients. A brief discussion on the significance of these changes in the context of UEA is provided with emphasis on onychomadesis, a finding usually related to graft rejection in this specific setting.

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Key words
nail changes, nails, onychomadesis, upper extremity allotransplantation, vascularized composite allotransplantation

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Introduction

Vascularized composite allotransplantation has emerged in the last 20 years as a novel surgical reconstructive procedure capable of replacing missing tissues whenever traditional reconstructive surgical procedures cannot provide adequate anatomical and functional tissue restoration. The most common type of vascularized composite allotransplantation is upper extremity allotransplantation (UEA). The International Registry on Hand and Composite Tissue Allotransplantation (IRHCTA) contains records of 74 cases [1]. UEA recipients often develop episodes of acute rejection (AR), and some of them eventually develop chronic rejection (CR) which often leads to graft loss. Both AR and CR manifest with a variety of skin lesions ranging from erythematous, asymptomatic macules to necrotic skin ulcerations. The nail unit is a cutaneous epithelial appendage, and as such, it may also be the target of the allograft rejection process. It has therefore long been anticipated that nail changes would be a manifestation of CR in UEA [2]. So far, nail changes have been

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reported in a small number of UEA recipients mostly during episodes of rejection, but these changes seem to be rarer and not so well known compared with the cutaneous ones. The IRHCTA contains records on nail growth only. Among the 74 UEA recipients, eight (11%) were reported to show 'diminished or abnormal' growth at some time during follow-up. We present here a patient with UEA who developed an AR episode 10.5 years postgraft, manifesting with onychomadesis which presented initially with a misleading clinical aspect of subungual proximal onychomycosis. On this occasion, we re-examined retrospectively the nail changes we have observed during follow-up of our series of eight UEA recipients, and reviewed the literature on nail changes reported in this specific patient group.

Patients and methods

Eight patients who had received an UEA (one single and seven bilateral) in our hospital and were followed up since 1998 were included in the study. Details on the surgical procedures, immunosuppressive treatment and functional outcomes for most of these patients have been reported previously [3,4]. All patients underwent careful physical skin examination during the first post-transplant months, thereafter at least once a year or more often if rejection was suspected, during the subsequent follow-up (mean 9.75 years, range 3–20). Skin biopsies were obtained at least at every yearly anniversary of each patient's surgery and whenever allograft rejection was suspected. Clinical photographs of the allografted upper extremities were taken at each follow-up visit.

Results

Index case

In July 2009, a 21-year-old Caucasian man received a bilateral hand allograft 5 years after having suffered post-traumatic amputation of his hands following an explosion. His maintenance immunosuppressive treatment consisted of tacrolimus, mycophenolate mofetil and steroids (ref. [4], patient n°5). During follow-up, he developed three episodes of AR within the first three post-transplant years which manifested either with multiple erythematous macules or with diffuse erythema over the allografts. These episodes were reversed with an increase of systemic immunosuppressive treatment and local application of clobetasol and tacrolimus ointments. Following the latest AR episode that occurred 31 months postgraft (Fig. 1), he developed alopecia areata of the scalp and the beard [5], but at that time his nails were not affected. In late December 2019, that is 10.5 years postgraft, he contacted us for a recent whitish discoloration of the proximal part of his right thumbnail, which was suggestive of subungual proximal onychomycosis (Fig. 2a); therefore, he was invited to report to our hospital for mycological examination. When arrived for his visit two weeks later, his nail lesion had changed. Physical examination showed onychomadesis, that is shedding, starting from the proximal nail matrix and the nail bed, of all nails of his right hand (Fig. 2b) and the left thumbnail. Concomitantly, the patient presented with erythematous macules over the forearms (Fig. 2c) and lichenoid, scaly papules on his proximal palms and the fingers around the nails. These findings were highly suggestive of allograft rejection, a diagnosis confirmed by histopathologic examination of a skin biopsy which showed changes of Banff grade III (lichenoid) AR (Fig. 2d). The patient received steroid boluses (500 mg each on three consecutive days). This treatment improved the skin lesions but the affected nails of the right hand and the left thumbnail were shed after some days. Microscopic examination of a shed nail plate did not show fungi upon PAS staining. The patient's nails are currently slowly regrowing but remain thin and brittle (Fig. 2e).

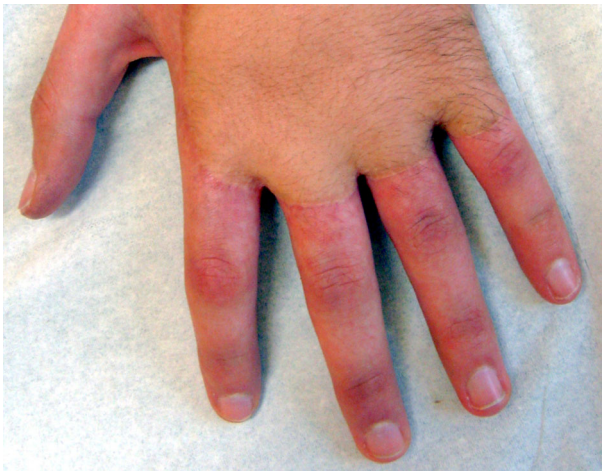

Figure 1 Patient n° 6 (index case). Acute rejection on postoperative month 31 (February 2011), manifesting with diffuse erythema of the allografted hand (fingers). The nails look normal (note that the back of the hand has received an autograft to cover a thermal burn sustained during the procedure of allotransplantation – the autograft has a normal colour).

Nail changes in the other UEA recipients

On the occasion of this patient's AR episode presenting with onychomadesis, we reviewed retrospectively the

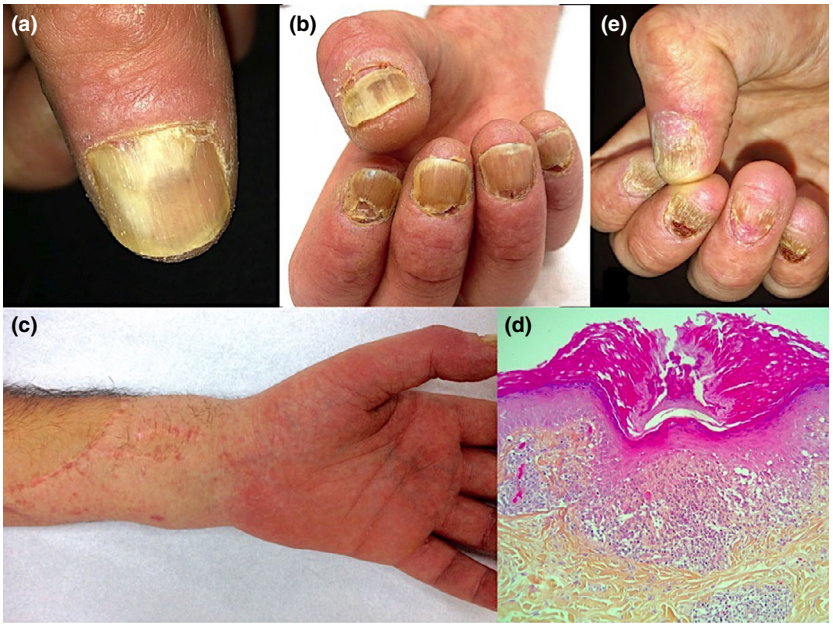

Figure 2 Patient n° 6 (index case). (a) Initial whitish aspect of the proximal thumbnail suggestive of proximal subungual onychomycosis (December 2019). (b) Onychomadesis of all nails of the right hand (mid-January 2020). (c) Erythematous macules on the allograft suggestive of AR, concomitant with onychomadesis (mid-January 2020). (d) Microscopic examination of the skin lesions shown in panel (c) shows changes of Banff grade III (lichenoid) rejection. (e) Regrowth of thin and brittle nails following onychomadesis (end of January 2020).

nail changes recorded in 8 patients with UEA performed and followed in our hospital (Table 1). Patient n°1 (with a single UEA, ref. [3]) discontinued the immunosuppressive treatment several months postgraft and progressively developed diffuse psoriasiform lesions on the hand and severe nail dystrophy (trachyonychia, brittling and exfoliation) (Fig. 3). The lesions were suggestive of CR and led to allograft removal during

Table 1. Nail changes observed in our patients with UEA.

Patient n°	Gender/age at Tx (years)	Tx date	Nail changes	Allograft outcome/latest follow-up visit (years)
1.	M/48	23/09/1998	trachyonychia, brittle nails, exfoliation following CR because of nonadherence to the immunosuppressive treatment (Fig. 3)	removed on POM29
2.	M/34	13/01/2000	thinning, longitudinal ridging of several nails starting from the 7th post-Tx year, persisting through the 20th post-Tx year, inconspicuous lunula (Fig. 4)	functional/20
3.	M/24	31/04/2003	periungual erythema with multiple small hangnails, median proximal longitudinal groove of the left thumb on 6.5th post-Tx year, isolated longitudinal melanonychia (9th post-Tx year) overlaid (10th post-Tx year) by a longitudinal fissure, persisting through the 11th post-Tx year (Fig. 5)	removed on POM 144 because of CR/GV
4.	F/27	19/02/2007	bilateral, keratotic/scaly cuticles of several nails with microhaemorrhages since POM6 – changes fluctuated over the years, variably associated with skin lesions of AR (Fig. 6)	removed at patient's request on POM 139
5.	M/29	04/07/2008	none	functional/12
6.	M/21	11/07/2009	(see 'case report') (Figs. 1 and 2)	functional/10.5
7.	M/41	05/11/2012	periungual erythema of some fingers – dry, fissured skin of the fingertips on POM1 (concomitant with skin lesions of AR), onychomadesis (3rd-5th R fingers) on POM 5 concomitant with skin lesions of AR (Fig. 7)	functional/7
8.	M/51	21/11/2016	none	functional/3

AR, acute rejection; CR, chronic rejection; F, female; GV, graft vasculopathy; M, male; POM, postoperative month; Tx, transplantation.

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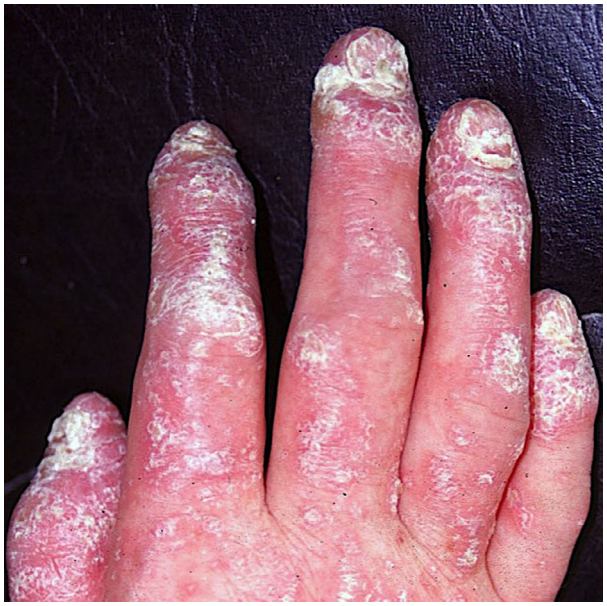

Figure 3 Patient n°1. Diffuse psoriasiform lesions of the hands with nail brittling and exfoliation in the setting of chronic rejection (24th postoperative month).

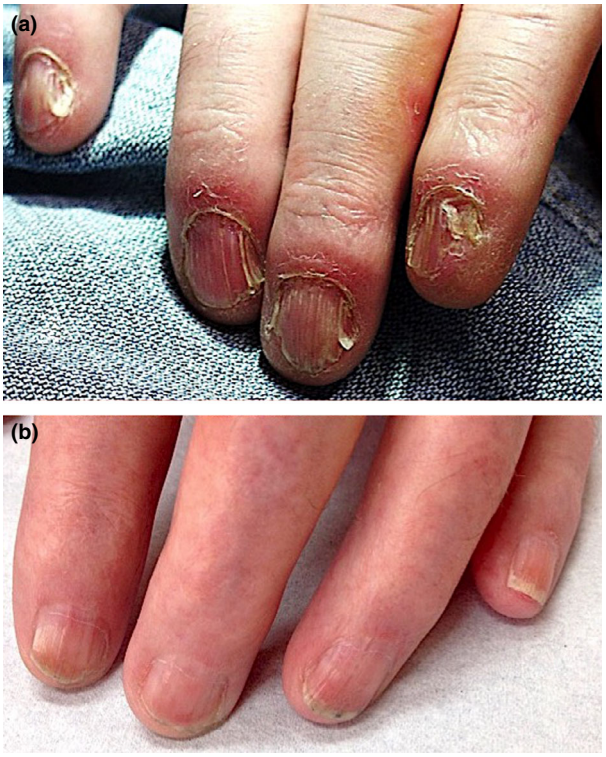

Figure 4 Patient n°2. (a) Longitudinal nail ridging, severe onychoschizia, erythematous eponychium and inconspicuous lunulae (85th postoperative month). (b) Slight ridging (more conspicuous on the left index finger), inconspicuous lunulae and thin nails at 20th post-transplant year.

postoperative month (POM) 29 [6]. Patient n°2 developed, starting from the 7th post-transplant year, thinning of most fingernails, longitudinal ridging, severe onychoschizia (i.e. splitting of the distal nail plate into layers) and occasional erythema of the eponychium (Fig. 4a). These lesions were variably present at each yearly follow-up visit and improved slightly over the years under treatment with a hardener nail lacquer but at the latest (20-year) follow-up visit, longitudinal ridging, nail thinning and inconspicuous lunula were present (Fig. 4b). This patient developed a few episodes of AR during the first post-transplant years, but his nail changes were not associated with obvious skin signs of AR; besides, the patient admitted some degree of onychophagia. Patient n°3 developed, at 6.5 years post-transplant, periungual erythema, a thickened cuticle and a short superficial median groove of the proximal two thirds of the nail of the left thumb; he had no other skin lesions suggestive of AR (Fig. 5a). At the 9-year follow-up, the patient was seen with an isolated longitudinal light-brown melanonychia (Fig. 5b). The following year, physical examination disclosed a nail fissure over the streak of melanonychia starting at the proximal area of the lunula and enlarging distally, reaching the free edge of the nail plate. The fissure persisted through the 11th postgraft year (Fig. 5c). The shape of the cuticle was suggestive of a self-induced repetitive trauma (habit tic for pushing back this area) which likely also produced the longitudinal melanonychia. Some months later, signs of CR started developing, manifesting initially with hand pain and then with necrotic ulcers over the digits, including the distal bed of the affected nails (Fig. 5d). This led to the progressive surgical amputation of the affected fingers and eventually of both allografts because of irreversible CR due to graft vasculopathy, which was histologically documented [7]. Patient n°4 developed, at the 6th post-transplant month, a scaly appearance of the cuticle of several nails on both hands (predominating on the right side), which contained black dots suggestive of microhaemorrhages (Fig. 6a). These changes fluctuated over the years, being sometimes absent or occasionally (namely at the 3rd and 4th postgraft year follow-up) associated with typical skin lesions of AR (Banff grades II and III) on the hands. The nail lunulae were generally inconspicuous (Fig. 6b). At the patient's request, the allografts were removed during the 11th post-transplant year, despite the absence of obvious clinical changes of CR [8]. Patient n°5 presented at POM1 with periungual erythema of some fingers associated with dry, fissured skin of the fingertips (Fig. 7a). These lesions were concomitant with more typical skin lesions of AR rejection.

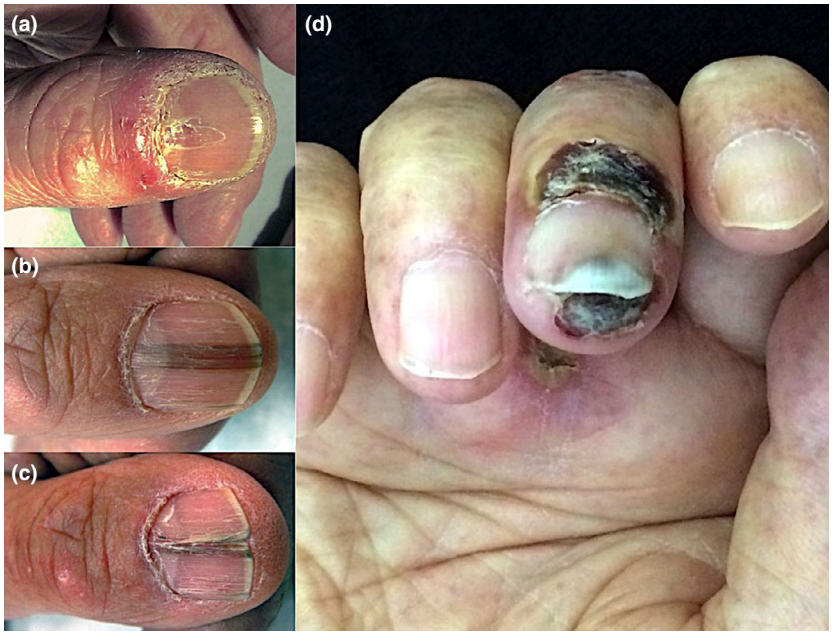

Figure 5 Patient n°3. (a) Periungual erythema with small hangnails, thickened cuticle and median groove of the proximal two thirds of the nail of the left thumb on 7.5th post-transplant year. (b) Isolated longitudinal light-brown melanonychia at 9th post-transplant year. (c) Persisting melanonychia overlaid by a longitudinal fissure at 10th post-transplant year (this persisted through the 11th post-transplant year). (d) Necrotic lesions on the fingertips and the distal nail bed because of CR with graft vasculopathy at 11th postgraft year.

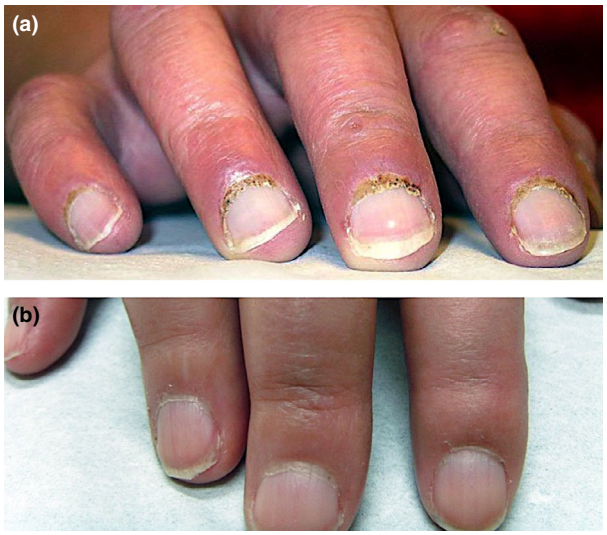

Figure 6 Patient n°4. (a) Hyperkeratotic, slightly scaly cuticles with microhaemorrhages (9th post-transplant month). (b) Regression of the nail lesions on the 6th post-transplant year. Note the inconspicuous lunula.

During the 5th POM, he developed onychomadesis of the 3rd-5th right fingers (Fig. 7b), which was associated with Banff grade II AR lesions on the forearms (Fig. 7c). Remarkably, this patient developed, during POM2, skin lesions of AR but at that time point his nails looked normal. Patients n°5 and 8 did not develop noticeable nail changes even though they developed some episodes of AR on their hands and forearms during the follow-up period (totalling 12 and 3 years, respectively).

Of note, no remarkable changes of other adnexa (namely hair follicles) were observed during the follow-up of our patients, even when they presented obvious nail changes; none of the patients complained of sweating troubles (hypohidrosis or hyperhidrosis).

Discussion

Similar to solid organ transplant recipients (OTR), patients with UEA can develop nail changes; however, these have received little attention in this setting. Nail changes have been mostly studied in renal transplant recipients, of whom 40–57% are reportedly affected by some nail disease. The more common of them include absence of lunulae, leukonychia, onychomycosis, Muehrcke lines and longitudinal ridging [9,10]. Some immunosuppressive drugs given to prevent allograft rejection have been incriminated in the post-transplant development of nail changes. For instance, rapamycin has been associated with leukonychia, slow growth, onychomalacia, onychorrexis, onycholysis, splinter haemorrhages, pyogenic granulomas and photo-onycholysis [11]. MMF has been associated both with onycholysis in OTR [12] and onychomadesis in patients with rheumatic diseases [13]. However, a direct role of drugs in the induction of nail changes is not always obvious. Some of the nail changes reported in OTR (such as longitudinal ridging, leukonychia and absence of lunulae) have also been observed in UEA recipients (14, 15, our patient n°2). These changes, including nail thinning which is sometimes noted in patients with UEA, are not

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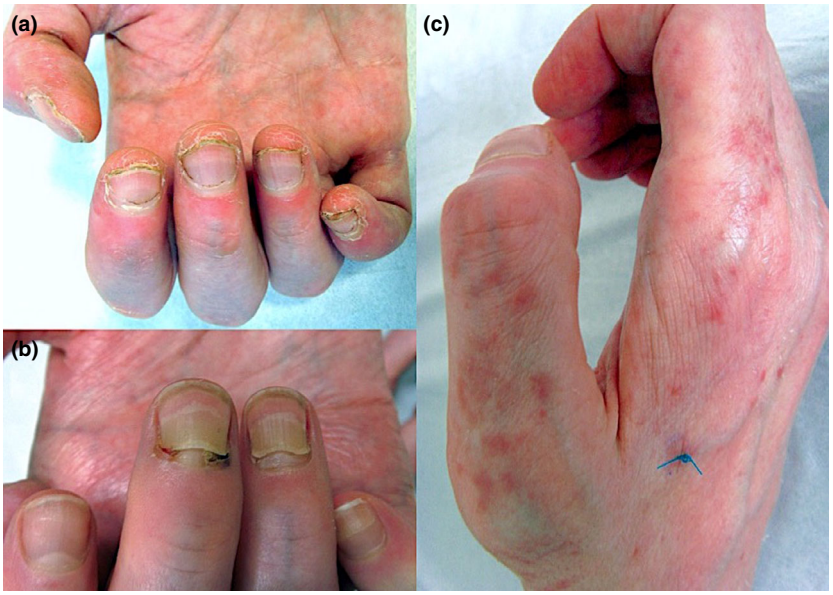

Figure 7 Patient n°5. (a) scaling and fissuring of the fingertips on 1st postoperative month. (b) Onychomadesis of the 3rd-5th fingers of the right hand concomitant with typical AR skin lesions on the dorsum of the hand (c) on the 2nd postoperative month.

Table 2. Nail changes reported in UEA recipients.

Type of change	References	Association with rejection
Onychomadesis	14, 15 our patients n° 6, 7	Yes
Nail thinning	14, 15 our patient n°2	uncertain
Nail ridging	15, our patient n°2	uncertain
Thickened cuticle	our patients n°3 and 4	uncertain
Cuticular microhaemorrhages (Maricq sign)	our patient n°4	uncertain
Trachyonychia, brittle nails	our patient n°1	Yes
Eponychium redness	19	no (HPV + wart)
Leukonychia	14, 15	uncertain
'Uneven' nails	18	Likely
'Loss of nails'	22	Yes
Onychoschizia	our patient n°2	uncertain
'Diminished or abnormal growth'	1	uncertain

uncommon in the general population so that the role of transplantation and/or immunosuppressive treatment in their genesis is difficult to assess. The scaly aspect of the nail cuticle containing microhaemorrhages (Maricq sign) we observed in our patient n°4 is observed in some systemic autoimmune diseases (namely dermatomyositis and systemic sclerosis) [16]. Our patient had no such a background. Interestingly, this patient developed over the same period of the follow-up capillary thromboses in the skin [17], and it seems likely that the microhaemorrhages of the nail cuticles were also because of capillary microthromboses.

Other changes we observed in our patients include dryness and scaly skin of the fingertips and a longitudinal melanonychia with subsequent nail fissuring, the latter possibly because of a habit tic for pushing back the cuticle. These changes were not always concomitant with skin lesions suggestive of AR and are therefore probably unrelated to rejection. Transverse leukonychia has been reported in two UEA recipients [14,15]; this resolved completely in one case and progressed with growth of soft nails in the other. In a series of 12 UEA cases from China, most patients reportedly developed 'uneven nails', with no further precision as to the timing and the aspect of nail changes [18]. In one patient, redness of the eponychium revealed an underlying HPV + wart [19].

The nail unit is an epithelial skin appendage contained in the UEA (along with hair follicles and sweat glands), and as such, it may become the target of acute or chronic rejection, similar to the remaining epithelial components of the skin. The finding of onychomadesis in two of our patients and three patients from the literature [14,15] strongly suggest that this change can be a manifestation of UEA rejection. Onychomadesis (from the Greek ονυξ: nail and μαδεσις: shedding) is a specific nail change characterized by separation of the nail plate from the matrix with persistent attachment to the nail bed and often, but not invariably, eventual shedding [20]. It can be idiopathic, hereditary, or because of neonatal trauma of birth. It can also be induced by

medications such as chemotherapeutic agents, pembrolizumab, antiepileptics, antibiotics, retinoids, lead and lithium, and may be associated with several cutaneous and systemic diseases, including autoimmune diseases and infections [18]. In our patients n° 5 and 6 onychomadesis occurred concomitantly with histologically documented cutaneous lesions of AR; in the first of them, the changes were severe, affected all nails and led to complete nail loss, whereas in the second patient, the changes were limited to 3 nails and did not result in complete nail loss. Of note in our patient n°5, the nail changes presented initially with a clinical aspect suspicious of proximal subungual onychomycosis (PSO), a recently described aspect of onychomycosis affecting usually immunosuppressed patients, especially those with HIV infection [21]. PSO was ruled out because of the negative PAS staining of the shed nail plate and the subsequent evolution into overt onychomadesis.

Onychomadesis has been previously reported in three other patients with UEA. In two of them, onychomadesis occurred at months 27 and 43 post-transplantation, respectively, and was associated with scaly skin lesions on the palms, leading to a diagnosis of 'atypical rejection'; the nails eventually regrew but remained initially dystrophic and soft in the long-term [14]. Onychomadesis was also reported in a stable UEA recipient 60 months post-transplantation in association with psoriasiform lesions of the palms. In this patient, the nails grew dystrophic but were completely lost at POM 68 [15]. In these three cases, the diagnosis of rejection was confirmed by histological examination of a nail-bed biopsy which showed dense lymphocytic infiltration characteristic of graft rejection. In this setting, the nail plate detachment is because of cytotoxic changes affecting the nail matrix, similarly to ungual lichen planus, which may closely mimic histologically Banff grade III skin rejection. This 'atypical' rejection was diagnosed in patients with heavy allograft use or repeated mechanical stress to the graft because of hand jobs and daily activity [14,15]. Nail loss has also been reported in another UEA recipient with CR without graft vasculopathy, although onychomadesis was not specifically mentioned in this patient [22]. Although onychomadesis can reportedly be induced by MMF [13], the responsibility of this drug in UEA-associated onychomadesis does not seem very likely; indeed, even though all UEA recipients with onychomadesis were receiving MMF when they developed this change, this did not always affect all fingernails as would be expected if it were a drug-induced side effect. In our two patients with bilateral UEA, onychomadesis affected some, but not all, fingers of both hands, a fact more consistent with the patchy appearance of AR episodes on the skin than with a drug-related effect.

In conclusion, nail changes have not been often mentioned after UEA, but seem to be not uncommon in this setting, as they were present at some time during follow-up in 6 out of 8 (75%) of our patients. Most of them are not specific to UEA and probably not related to rejection as they are observed also in OTR and in the population at large. By contrast, onychomadesis seems to be more specific to UEA as it may be associated with (acute or chronic) allograft rejection (Table 2). We propose that careful examination of the nails should be performed during monitoring of UEA recipients. Study of a larger number of cases will allow a better understanding of the significance of nail involvement in the outcome of upper extremity allografts.

Authorship

JK: followed dermatologically all patients, analysed the data and wrote the paper. PP, LB and EM: followed clinically all patients and contributed to data collection. AG: performed some of the transplantations and followed the patients. RB: critically reviewed the article and participated in data analysis. All Authors read and approved the submitted manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

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