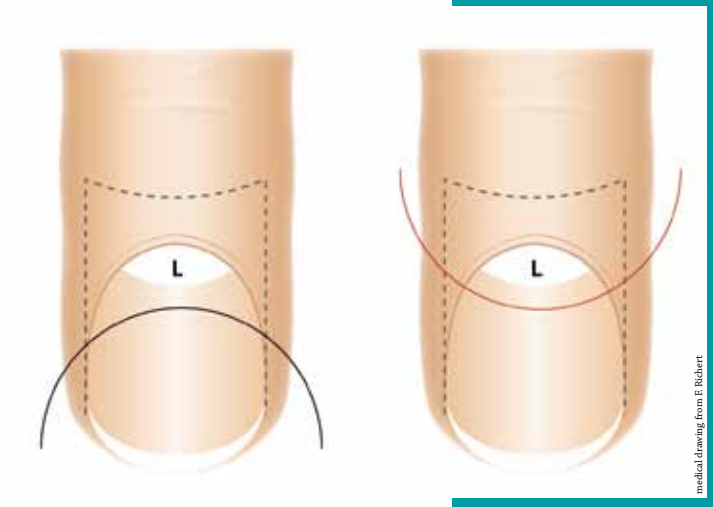
English edition 2013

n°6

The nail



medical drawing from F. Richert

What's new ?

European Nail Society

The Official Journal of the European Nail Society

Pierre Fabre DERMATOLOGIE

EDITORIAL

Dear Colleagues

L'Ongle - Quoi de Neuf? and The Nail - What's New? are respectively in their 9th and 6th year of edition and since 2012 have become the Journal of the European Nail Society.

Robert Baran made this possible due to his enthusiasm, dynamism, mastery and leadership, when he invited several European dermatologists, all interested in nail pathology, to participate in this Journal. There are currently nine collaborators and it is a great honor for me to have constantly been among them since the first edition. Today I invite you to read this new edition, which you will certainly keep close to you as an aid in your daily clinical practice.

I wish to especially acknowledge Pierre Fabre, who supported this project from the very beginning and also give great thanks to Nicole Baran for her excellent work in providing logistical support to all the co-authors throughout the months before publication.

The interest in nail pathology has been growing, not only for dermatologists, but also, among others, for pediatricians and general practitioners. The knowledge of different diseases, both immuno-inflammatory, infectious and neoplastic, their differential diagnosis and therapeutic alternatives is now essential and requires understanding and ability, together with medical clinical practice for the treatment to be successful.

This Edition contains several papers on different topics. Based on six papers, David de Berker discusses the treatment of nail psoriasis from topical therapies to biologics. Robert Baran reminds us that ultra-sonography is a very useful tool in the diagnosis of nail psoriasis and that it is not costly. However, he draws our attention to the fact that distal phalangeal bone edema can only be detected by resonance imaging that is able to predict development of onycholysis and hyperkeratosis. Véronique Blatière reviews different etiologic reasons for chromonychia. She emphasizes that transverse orange-brown chromonychia can be a new clue for the diagnosis of Kawasaki disease. A very useful revision of diagnostic criteria, nail symptoms and treatment approach of this disease has been drawn up. Bruno Fouilloux has written a meticulous review on the interest of laser in the treatment of onychomycosis. He specifies that randomized controlled trials are needed to determine the long-term success of these devices. Bianca-Maria Piraccini emphasizes the importance of adequate sampling for mycological study in onychomycosis, and made a revision of new topical treatments. Bertrand Richert summarizes papers concerning the lifetime risk of carcinomas due to UV nail lamps, which however seems to be low. He reminds us of the superficial acral fibromyxoma and the conservative approach treatment of subungual melanoma in situ.

Jose Maria Mascaro discusses the role of nail fold capillaroscopy, not only in connective tissue diseases, but in other dermatological and non dermatological diseases. Eckart Haneke details on how to early diagnose subungual melanoma and onycholemmal carcinomas. He also reviews how to manage ingrowing nails. Finally I was in charge of reviewing the risk factors, and provided clues, for an early diagnosis of nail apparatus melanoma, as well as revising skin and nail side effects of recent anti-cancer agents.

There is also a series of very interesting clinical cases of all contributors at the end of the journal.

I sincerely hope that you will enjoy this new edition of "The Nail - What's New?" coordinated by Robert Baran and Bertrand Richert, as much as I have.

Osvaldo Correia

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contents

The nail - What's new ? n° 6

Condensed selected articles with commentary

Robert BARAN

Nail, joint & psoriasis

The importance of nail disease on subjects with psoriasis is being increasingly recognized.

Aydin SZ, Castillo-Gallego C, Ash ZR et al. Ultrasonographic assessment of nail in psoriatic disease shows a link between onychopathy and distal interphalangeal joint extensor tendon enthesopathy. Dermatology 2012; 225: 231-5.

The authors compared ultrasonography (US) with the mNAPSI (Nail Psoriasis Severity Index) to investigate the nail plate-nail matrix and adjacent tendons in subjects with psoriatic nail disease and to test the hypothesis that the nail involvement was specifically linked to extensor tendon enthesopathy.

Nail plate findings by US and comparison with clinical assessment

The absolute agreement between US and clinical assessment in the 169 nails of the psoriatic patients was 76.3%. US detected abnormalities in 10 nails where clinical examination was normal. Conversely, US failed to demonstrate any lesions in 30 nails despite the presence of a positive clinical finding.
Nail thickness was greater in patients in the psoriasis group compared to control of heathy nails (HC). Nail thickness was higher in those nails with clinical abnormalities.

Nail matrix findings

Entheseal thickening of the extensor tendon insertion region was more frequent in patients in whom there was an abnormality in the adjacent nail by physical examination. Onycholysis **(Fig 1)**, pitting and nail crumbling were found more frequently in patients with extensor tendon entheseal thickening.
The thickness of the matrix was higher if there was clinical nail disease in both Psoriasis and Psoriatic Arthritis (PsA). In patients with clinical distal interphalangeal joint (DIP) disease (with tenderness or swelling), extensor tendon thickening was more frequent in active DIP joints vs non-active DIP joints. The thickness of the skin and the matrix

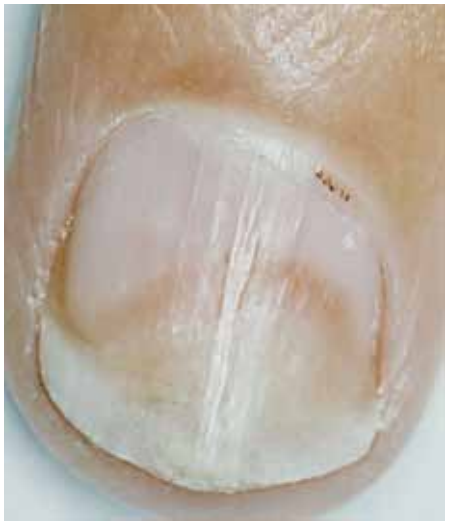

Fig1- Onycholysis. © R. Baran

were higher in those with clinical DIP disease whereas nail thicknesses were similar.
Both US and clinical examination were broadly similar for the assessment of the nail plate region. In the evaluation of the nail matrix region the authors noted an association between extensor tendon enthesopathy and nail disease. This enthesopathy was specifically associated with nail disease, but not clinical PsA. These findings are relevant for the development of US for the assessment of nail disease and also point towards the importance of the enthesis in nail involvement.
The link between enthesopathy on US and clinical nail disease was not confined to pitting, a recognized matrix specific abnormality, but was also seen with onycholysis (thought to be a nail plate lesion) which therefore would not be expected to be related to extensor tendon disease. These findings raise the possibility that nail pain and loss of function seen in the dermatological setting may, in part, be related to microenthesopathy.
Another noteworthy finding of the present study was that DIP enthesopathy was associated with both epidermal thickening and dermal oedema. This is interesting since it suggests a very close link between the pathology in the skin and the adjacent enthesis.

Nail, joint & psoriasis

Robert BARAN

Ash Z R , Tinazzi I, Castillo-Gallego C et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis 2012; 71: 553-56.

Psoriasis affects approximatively 2% of the population and up to 30% of these will develop psoriatic arthritis. Now that effective therapies for the suppression of PsA exist, the early recognition of PsA has important consequences for optimal patient management.
It has been suggested that enthesitis is the primary lesion that underscores the diverse skeletal manifestations of PsA. It has also been demonstrated that subclinical enthesopathy and associated osteitis is present in up to 50% of patients with psoriasis with no arthritis. Another stream of research has shown that the presence of nail disease is a harbinger for the future development of PsA. Combined clinical and imaging observations suggest that there may be a link between systemic enthesopathy and psoriatic nail disease.

Ultrasonography

Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment may occasionally contain hyperechoic foci consistent with calcification, seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity. Thickness measurements and erosions were scored quantitatively, except the thickness of the common extensor tendon which was assessed semi-quantitatively. The thickness of the entheses was measured at the level of insertions in longitudinal scans.

Discussion

Given that nail disease is a predictor for PsA evolution and that the nail is functionally integrated with a network of entheses about the distal interphalangeal joints, the authors tested the hypothesis that nail involvement in psoriasis was linked to a more extensive subclinical enthesopathy. Their findings confirmed that subclinical enthesopathy was common and was specifically related to nail disease. In addition more extensive nail involvement correlated with more severe enthesopathy scores.
In conclusion, this study confirms that enthesopathy is common in psoriasis patients without clinical arthritis.

Dalbeth N, Pui K, Lobo M et al. Nail disease in psoriatic arthritis: Distal phalangeal bone edema detected by magnetic resonance imaging predicts development of onycholysis and hyperkeratosis. J Rheumatol 2012; 39: 841-3.

Nail disease is a common feature of psoriatic arthritis (PsA). Cross-sectional magnetic resonance imaging (MRI) studies have shown that nail involvement detected by MRI is present in most patients with PsA, and that MRI nail disease is strongly associated with abnormalities in the corresponding distal phalanx (DP) and associated structures.
At baseline, nail pitting was not associated with MRI changes in the DP. However, nails affected by onycholysis and hyperkeratosis were more likely to have corresponding DP bone erosion and proliferation on MRI.
Follow-up assessment of 80 fingernails at 1 year showed 13 (16%) with pits, 20 (25%) with onycholysis, 8 (10%) with hyperkeratosis **(Fig 2)**, and 2 (3%) with dystrophy. At baseline of the 67 nails without pits, 10 (15%) developed pits; of the 61 nails without onycholysis, 4 (7%) developed onycholysis; and of the 72 nails without hyperkeratosis, 4 (6%) developed hyperkeratosis. There was no relationship between development of nail pitting and corresponding DP disease on baseline MRI. However, nails that developed onycholysis were more likely to have corresponding DP Bone marrow edema (BME) on baseline MRI was compared with nails that did not develop onycholysis (50% vs 11%).

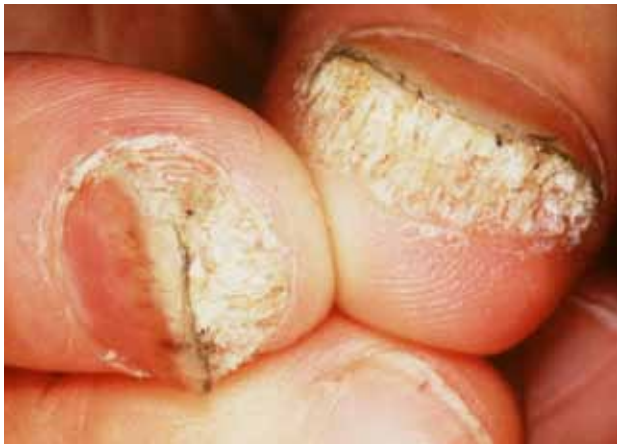

Fig2- Subungual hyperkeratosis. © H. Roger, Clermont-Ferrand

Robert BARAN

Similarly, nails that developed hyperkeratosis were more likely to have corresponding DP BME and erosion on baseline MRI compared with nails that did not develop hyperkeratosis.
This study demonstrated a relationship between DP bone disease and psoriatic nail disease in patients with PsA. Further, certain features of psoriatic nail disease, onycholysis and hyperkeratosis, were strongly associated with DP disease. BME is also strongly associated with bone erosion in patients with erosive PsA, and biologic therapies that target BME and prevent erosion in PsA, also prevent nail disease.
The authors' data provide further evidence of the close relationship between adjacent bone and nail disease in PsA, and support the hypothesis that inflammation at the DP is central in the development of psoriatic nail disease.

Soscia E, Sirignano C, Catalano O et al. New developments in Magnetic Resonance Imaging of the Nail Unit. J Rheumatol 2012; 39 suppl 89: 49-53.

Nail involvement was present in almost all cases studied, even in those without clinically evident onychopathy. Nail thickening with or without surface irregularity was the most common finding, and MRI nail changes were more marked in patients who had an increased NAPSI. The authors demonstrated the constant overlap between the presence of nail alteration and distal phalanx involvement. The involvement of the DIP joint was constantly present instead of a smaller percentage of patients showing usually distal phalanx involvement. This point suggested a primary involvement of entheses linking nail to distal phalanx and supported the idea that the involvement of the DIP joint could be secondary to that of the distal phalanx.

Usefulness in clinical practice of MRI study of the nail units of patients with arthritis

The traditional radiographic plain film study is limited to the evaluation of bone structures. MRI allows the evaluation of bone, soft tissue and, if adequately performed, the nail.
In the case of PsA, the MRI study of the nail unit revealed that nail involvement is the main lesion for the development of the distal phalanx damage and consequently of DIP joint arthritis. The authors also demonstrated that all patients with psoriasis, even in the absence of clinically evident onychopathy, show characteristic MRI nail changes.

Magnetic resonance imaging

MRI of the finger, in the absence of ionizing radiation, is useful for the evaluation of patients who have borderline psoriasis.
The nail margin can be evaluated with MRI by putting petroleum jelly on its outer surface to outline the nail profile and to allow easy evaluation of the phalanx bone alterations and tendon involvement. The sensitivity of MRI in revealing bone erosion, bone edema, and soft tissue inflammation is higher than with plain radiographic studies. The association with intravenous contrast medium administration is widely used to demonstrate synovial inflammation in RA and to increase the sensitivity in identifying bone alterations, before their morphological evidence.

Palmou N, Marzo-Ortega H, Ash Z et al. Linear pitting and splinter haemorrhages are more commonly seen in the nails of patients with established psoriasis in comparison to psoriatic arthritis. Dermatology 2011; 223: 370-73.

Nail involvement in psoriasis may have two basic patterns, one related to epidermal changes such as subungual hyperkeratosis and a second pattern that might be associated with the entheses that anchor the nail matrix and nail plate region. In the latter case, the authors hypothesised that the involvement of the nail matrix by the inflammatory process might contribute to lesions, such as pitting, in a linear pattern consistent with the "finger-like" attachment of the ligamentous structures linking the nail to the extensor tendon and distal interphalangeal joint capsule.

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However, in the nail matrix, both pitting **(Fig 3)** and linear pitting were seen more frequently in psoriasis than in PsA. Linear pitting was seen in 8% of PsA cases and in 25% of psoriasis cases. There were no differences in the rates of leuconychia or nail matrix crumbling between the groups.
In the nail plate, splinter hemorrhages were seen in 5.8% of PsA cases and in 21.2% of psoriasis cases. There were no differences in the rates of onycholysis or subungual hyperkeratosis between the groups.

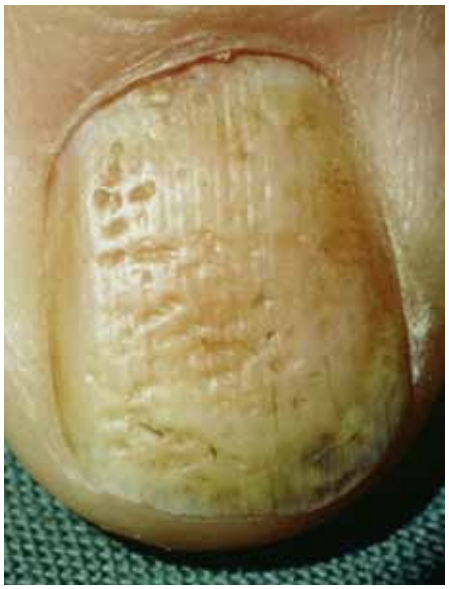

Fig3- Nail pitting. © R. Baran

COMMENTARY R. BARAN

Psoriatic nail involvement is a common finding in Psoriasis.[1] At least 70% of patients with PsA present nail changes. The typical patient complains of persistent joint pain which may be accompanied by early morning stiffness, usually lasting more than half an hour. Stress pain, joint line tenderness and effusion in an asymmetrical pattern are common.[2] An interesting point is the disparity between the lesions that affect the matrix where they are transient or the nail bed, where they are permanent.
Nail dystrophy in psoriasis patients can be an indicator of ongoing involvement of the distal phalanx and individuals with psoriasis have an increased risk of developing PsA in their lifetime. Psoriasis may be present, but hidden and misdiagnosed. Scalp lesions, intergluteal/perianal psoriasis and nail dystrophy are significantly associated with an increased risk of developing PsA. Larger more severe psoriatic lesions are partly consistent with previous studies, suggesting that they are associated with PsA.[3]
Corticosteroid use was associated with an increased risk of developing PsA.[4]
The nail is functionally linked to the distal phalanx and several distal interphalangeal structures, including extensor tendon fibers and the collateral ligaments and the nail should be seen as a musculoskeletal appendage with a structure termed "enthesis organ". The finding of entheseal imaging abnormalities in asymptomatic psoriasis patients dovetails with the work of McGonagle who has put forth the concept that enthesitis is one of the first steps in the development of PsA.[5-6]
"The five targets"[7] of a sonographic spectrum found in PsA patients include joint and tendon inflammation, enthesitis, new bone formation, severe osteolysis and overlapping of all of these. Ultra-sonography is a very useful tool that is not costly **(Fig 4a,b - p12)**.
However distal phalangeal bone edema can be detected only by magnetic resonance imaging that is able to predict development of onycholysis[8, 9] and hyperkeratosis.[10, 11]
Recent reports have suggested that there may be a direct link between inflammation in DIP and nail changes.[12,13]
The nail is attached to the bone with several entheses that in psoriatic patients could diffuse inflammatory changes from nail to bone of the distal phalanx through cellular fat tissue.[14]
According to Soscia et al.[15] MRI of the nail may play a role in diagnostic differentiation in the case of patients with other inflammatory conditions such as rheumatoid arthritis (RA). In patients with RA, MRI has revealed the involvement of the DIP joint, but it does not show alterations of the nail. In addition, MRI may be able to allow differential diagnosis between PsA and nodal osteoarthritis in patients with associated skin psoriasis.

Nail, joint & psoriasis

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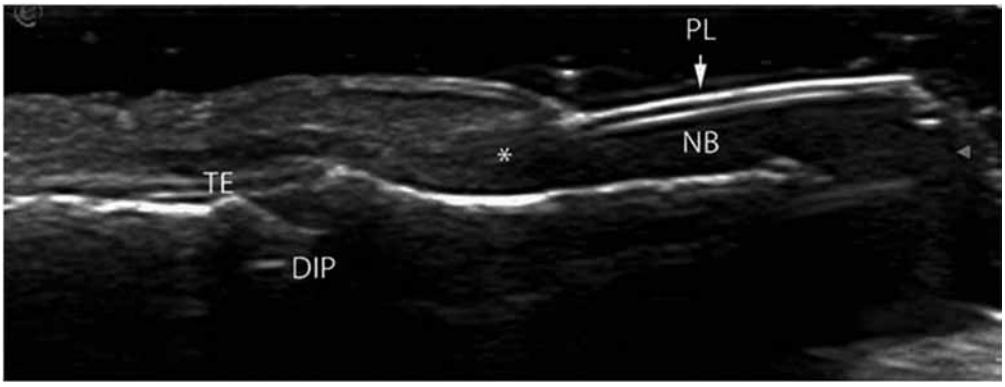

Fig4a- Sonography of normal nail . © X. Wortsman, Chile

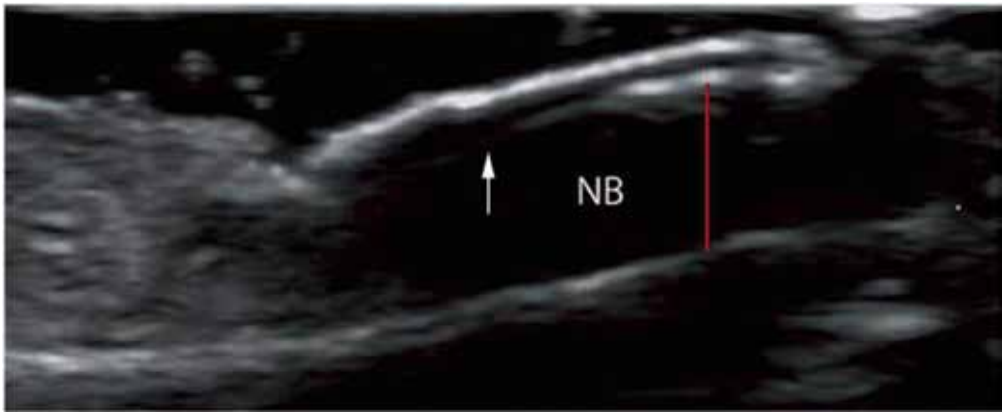

Fig4b- Sonography of psoriatic nail. © X. Wortsman, Chile

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Chemical avulsion

M. Lahfa, C. Bulai-Livideanu, R. Baran, JP. Ortonne, B. Richert, A. Tosti, BM Piraccini, JC Szepietowski, V. Sibaud, H. Coubetergues, JJ Voisard, C. Paul. Efficacy, safety and tolerability of an optimized avulsion technique with Onyster® (40% urea ointment with plastic dressing) ointment compared to bifonazole-Urea for removal of the clinically infected nail in toenail onychomycosis: a randomized evaluator-blinded controlled study. Dermatology 2013; 226:5-12

The goals for onychomycosis treatment are mycological cure and a normal looking nail. The ways to reach them can be obtained via the oral or topical route. However, the side-effects of systemic drugs and drug interactions in subjects taking several medications promote the use of topical drugs. These are especially recommended for treatment of patients with mild to moderate onychomycosis, i.e. when less than 50% of the nail is infected without matrix involvement.

Distal-lateral subungual onychomycosis (DLSO) is the most common variety. The fungus, most often involves *Trichophyton rubrum*, comes from the soles of the feet, reaches the pulp and then the hyponychium where the plate separates from the underlying tissue and finally invades the nail bed. In an ultimate stage the dermatophyte penetrates into the deep layers of the nail keratin. Consequently, this type of onychomycosis is a disease of the nail bed. The major therapeutic challenge is to deliver the active substance to the site of infection through the nail plate in order to reach the fungal reservoir to promote drug penetration and reduce the fungal infection. The best way, however, is to remove the infected portion of the plate to promote nail penetration and reduce the fungal load. Therefore, partial nail avulsion is used as adjunctive therapy to topical and or oral antifungal treatment.

As a prerequisite to antifungal treatment, chemical avulsion with 40% urea products is now recommended in the USA for moderate to severe nail involvement and in France for onychomycosis caused by dermatophytes *(Recommendations for the management of onychomycosis in adults - National Guidelines Clearinghouse 2003; Société Française de Dermatologie - Recommandations 2007)*. The mechanism of action of 40% urea consists of weakening the affected nail plate - nail bed attachment. This means that normal nail is not affected while the fungal portion is easily detachable.

Several studies evaluating the efficacy of 40% urea for nail avulsion have been reported. The combination of 40% urea and 1% bifonazole associated with *patient*-driven nail avulsion has been available for several years in some European countries (Amycor Onychoset® in France, Mycopor Onycoset® in Germany) but a new ointment containing 40% urea with plastic dressing (Onyster®) has been developed to promote *physician*-driven pathological nail avulsion in onychomycosis. This last treatment appears as a prerequisite to topical therapy of onychomycosis. Lahfa and al study assessed efficacy of these two treatments in DLSO.

It was conducted in 105 randomized patients (53 in Onyster® group and 52 in the bifonazole-urea group) with a diagnosis of onychomycosis of the great toenail. This target nail plate had to show more than 12.5% of the clinically infected area and at least 2 mm of the proximal target nail free of infection **(Fig 1)**. Both products were applied to the

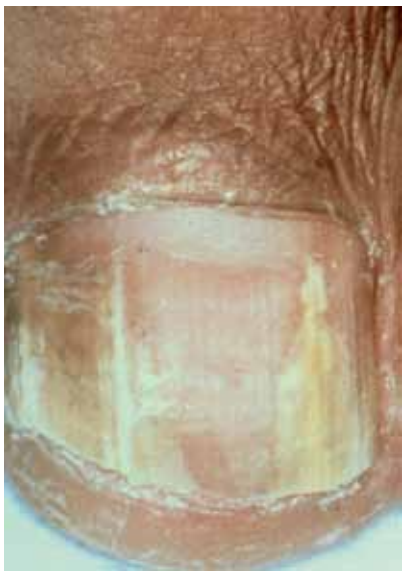

Fig1 - Dermatophytic nail *(Trichophyton rubrum)*

Chemical avulsion

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affected nail for three weeks **(Fig 2)**. Each nail is covered with an occlusive dressing **(Fig 3)**. In accordance with the summary of product characteristics, patients treated with bifonazole-urea had to soak daily the nail in warm water for about 10 minutes after removal of the dressing. Thereafter, patients were instructed to remove the softened part of the infected nail, using the scraper provided with the product. The medication was repeated every day for a maximum duration of three weeks. In patients treated with Onyster®, nail debridement was performed by the investigator only once on the 21st day **(Fig 4)**. The patients were advised not to file, clip or change the target nail.

The primary efficacy criterion was defined as completed removal of the infected target nail plate area at D21 centrally assessed by a blinded dermatologists expert panel (not investigators) on standardized photographs taken at D0 and D21.

The success rate at 21st day showed complete removal of the clinically infected target nail plate area and was observed in a significant higher proportion of patients in the Onyster® group (61.2%) compared to the bifonazole-urea group (39.2%, p=0.028). More patients in the Onyster® group assessed the use of this treatment as satisfying/ very satisfying compared to the bifonazole-urea group (92.2% vs 74.5%, p=0.017).

COMMENTARY

In this first randomized controlled study, evaluating the efficacy and safety of two chemical nail avulsion methods to remove infected toenails with onychomycosis, Onyster®, followed by a trained physician debridement, demonstrated its superior efficacy in comparison with bifonazole-urea treatment combined with daily scraping by patients themselves **(Fig 5)**.

In the absence of nail debridement, the cure rates associated with topical antifungal monotherapy using stringent criteria such as complete cure have been rather disappointing or, at least controversial.

This was the objective of the second study to try to compare both therapies.

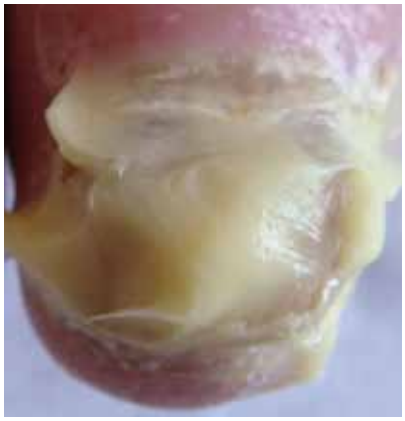

Fig2 - Application of the 40% urea ointment

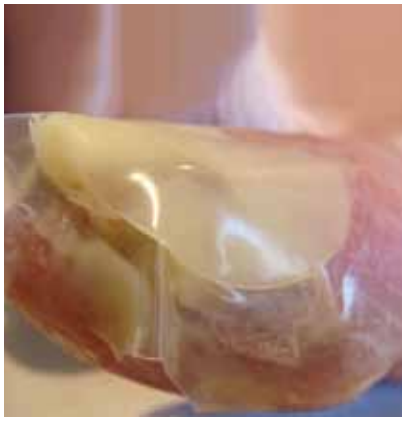

Fig3 - Same toe covered with an occlusive dressing

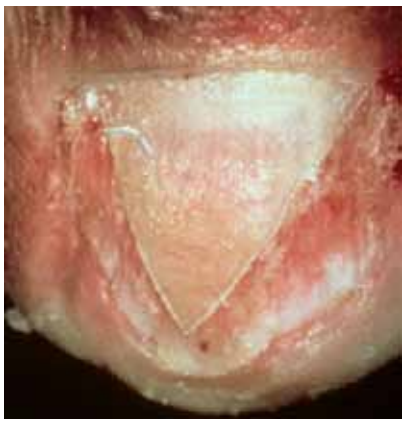

Fig4 - At Day 21, nail debridement performed by the investigator

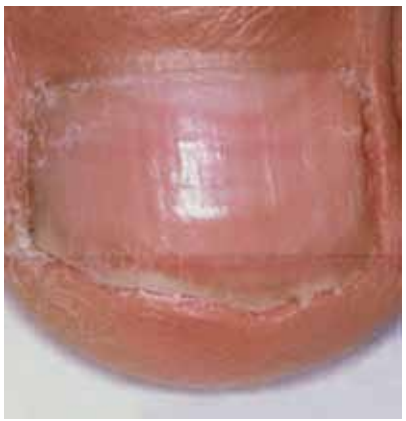

Fig5 - Complete cure of the nail

Chemical avulsion

Robert BARAN

Paul C, Coustou D, Lahfa M, Bulai-Livideanu C, Doss N, Mokthar I, Turki H, Nouira R, Fazaa B, Ben Osman A, Zourabichvili O, Cazeau C, Coubetergues H, Picot S, Bienvenu AL, Voisard JJ. A multicentre, randomized, open label, controlled study comparing the efficacy, safety and cost-effectiveness of a sequential therapy with RV4104A ointment, ciclopiroxolamine cream and ciclopirox film-forming solution with amorolfine nail lacquer alone in dermatophytic onychomycosis. Dermatology 2013 (DOI:10.1159/000353667).

As in the previous study debridement was considered to be the first step for onychomycosis therapy, in their article Paul and al. devised a sequential (SEQ) treatment with:

1- chemical nail avulsion with Onyster® for three weeks followed by
2- ciclopirox cream for 8 weeks and
3- ciclopirox nail lacquer for 25 weeks vs the standard treatment with amorolfine (AMO) nail lacquer applied twice weekly for 36 weeks in dermatophytic onychomycosis due to *Trichophyton rubrum*. The patients had to have a big toenail infection DLSO type, sparing the matrix area and showing between 25 and 60% of clinically infected nail area and with 2mm of unaffected proximal target nail area.

The primary efficacy variable was the complete cure at week 48 in the intent-to-treat (ITT) population. Complete cure was defined as the combination of clinical cure (i.e. disappearance of all lesions on each nail or residual disease of no more than 10% of the original total diseased surface) and mycological cure (i.e. negative direct microscopy and negative culture). This clinical cure definition given by the authors is important as some others consider the residual 10% disease left as "clinical success". Secondary efficacy assessment included: clinical cure at week 11, 24 and 36 defined as the disappearance of all lesions on the target nail or residual disease of no more than 10% of the original total diseased surface. Safety was assessed through adverse event monitoring. Global assessment of local tolerability was evaluated at week 3, week 11, week 24 and 36 using a 4-points scale: very good, good, poor and very poor.

142 patients were randomized and constituted the ITT population: 71 received amorolfine (AMO group) and 71 received sequential therapy (SEQ group). Overall, 95.1% of the patients completed the study. Discontinuation rates were higher in the AMO group (7%) than in the SEQ group (2.8%) mainly due to the lack of efficacy (4.2%) in the AMO group vs 0% in the SEQ group. The compliance was similar in both groups. At week 48 SEQ treatment resulted in a significantly higher complete cure rate 36.6% compared with AMO (12.7%). The local tolerability was good for more than 90% of patients in each group at each visit. Assessed at week 36, local tolerability was "very good" and "good" respectively in 97% and 3% in the AMO group compared to 94.3 and 5.7% in the SEQ group.

COMMENTARY

The use of antifungal nail lacquer has long been the only alternative for topical treatment of onychomycosis. This study has shown that a sequential antifungal treatment with chemical avulsion with Onyster® drastically improves onychomycosis treatment efficacy rates compared to nail lacquer alone. These results are new a challenge for dermatologists in onychomycosis treatment and should help them to change their prescribing habits in this affection.

For years, I made a plea for nail avulsion (at least, partial) as a first step in the management of fungal infection. The use of 40% urea ointment with plastic dressing is certainly a major improvement of the treatment of onychomycosis.

Véronique BLATIÈRE

Chromonychia

Pal P, Giri PP. Orange-brown chromonychia, a novel finding in Kawasaki disease. Rheumatol Int. 2013; 33: 1207-9.

A transverse orange-brown chromonychia has been found to be a high value-added clue for the diagnosis of Kawasaki disease. It appears early, between the fifth and eighth day of fever onset and then it migrates distally and fades at 2 weeks; a complete disappearance setting in within the next 2 or 3 weeks. The color change is better appreciated on fingernails than on toenails. First described by Lindsley, this sign has been found in the authors' series in 29 patients out of 40 children under 10 years old, who fulfilled the criteria of Kawasaki disease. It has been observed in systemic arthritis and hemophagocytic lymphohistiocytosis. The other nail symptoms described in this childhood vasculitis are: periungual desquamation, transverse leukonychia, Beau's lines, onycholysis, onychomadesis, leukonychia partialis and spontaneously resolving pincer nail deformity.

Harada K, Morohoshi T, Ikeda T, Shimada S. A patient with pseudochromhidrosis presenting with pink nails. J Am Acad Dermatol. 2012; 67 (2):e74-5.

The authors report a case of pink discoloration of a female toenail **(Fig 1)**.The patient had no medical history and routine laboratory tests were normal. The clinical examination revealed a pink coloration of her cheeks, palms (the gloves she had worn for half a day turned pinkish red) and toenails. A bacteriological analysis of the skin swab on her face and extremities was positive to *Serratia marcescens*, a chromogenic bacterium whose pigment is called prodigiosin. She was cured by oral treatment (cefcapenepivoxil 300mg daily) associated with topical application (1% nadifloxacin cream, twice daily). This led to complete clearance of the red staining in 3 months. Prodigiosin derivatives were found in the patient's sweat, allowing the diagnosis of pseudochromidrosis (sweat colored by exogenous origin) compared to apocrine chromhidrosis (increased number of lipofuscin granules within the secretory apocrine cells) .

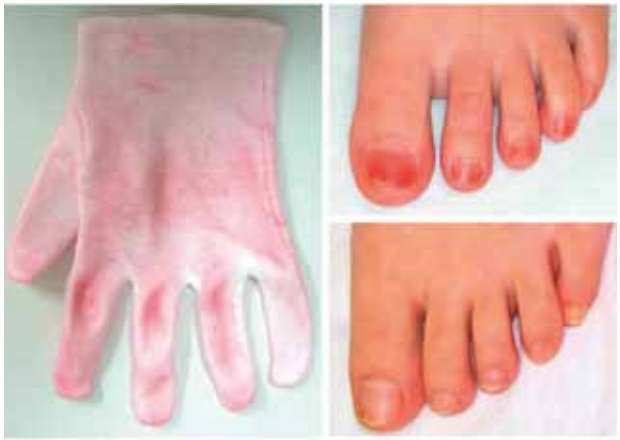

Fig1 - Pink colour of the toenails and pink coloration of the gloves. © K.Harada

Takci Z, Ozoguz P. Nail discoloration due to tinzaparin sodium. Cutan Ocul Toxicol. 2012; 31:332-4.

In this article, the authors describe a brownish black diffuse nail discoloration occurring after a treatment with 10,000 IU tinzaparin sodium subcutaneaous injections, once daily for 8 weeks. Tinzaparin had been prescribed for recurrent pregnancy loss. The nail discoloration increased over time, spreading to all nails and, began to regress when the drug was stopped after the birth. At 5-month follow-up, the pigmentation remained only at the distal edge and finally disappeared 6 months after drug discontinuation. There was no other pigmentation on the whole body.
They discuss the imputability of tinzaparin as a drug-induced nail hyperpigmentation because the patient had experienced no nail pigmentation during her previous pregnancies. Her only affection was a thrombophilia diagnosed after the last miscarriage and for which she had taken no medication.

COMMENTARY V. BLATIÈRE

Orange

Kawasaki disease is an acute systemic vasculitis of unknown cause that primarily affects children under 5 years of age. It was first described in Japan in 1967 by Dr. Tomisaku Kawasaki and colleagues. Delays in accurate

Chromonychia

Véronique BLATIÈRE

diagnosis lead to increased mortality and morbidity from complications of Kawasaki disease. The diagnosis is based on the same clinical features originally used to describe the disease more than 30 years ago.[1] These clinical findings are non specific and are commonly found in many pediatric infectious and immunologic diseases **(Table 1, p18)**. Moreover they may be absent or may evolve over many days after fever onset. Hence, Kawasaki disease presents a diagnostic challenge, and a high index of suspicion is required for early diagnosis and initiation of treatment **(Table 2, p18)**.

Kawasaki disease should be considered in a child who has persistent fever but neither focus of infection, nor response to antimicrobial treatment or other clinical or laboratory features of Kawasaki disease **(Table 3, p18)**. If a child is suspected of having acute Kawasaki disease he has to be referred to a pediatric cardiologist for cardiac assessment and follow-up.

In their article, Pal and Giri[2] suggest incorporating orange-brown chromonychia to the clinical existing criteria of Kawasaki features.

It has recently been discovered that urine proteomes of patients with Kawasaki disease, but not those with mimicking conditions, were enriched for potential markers of endothelial and myocardial injury (talin, filamin, desmoglein, obscurin and titin), leukocyte activation (AMICA1, CAECAM, CXCL12, GDF15 and LAIR1), pathogen immune recognition (DMBT1, ABCB9) and cytokine regulation (CSMD3, meprin A).[3]

It was shown in the serum that meprin A and filamin C are specific and sensitive markers of Kawasaki disease using commonly available ELISAs. This enables their clinical use to improve the accuracy and timeliness of diagnosis of Kawasaki disease.

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Pink

Harada et al.[1] report a case of pink discoloration of a female's toenails with pseudochromhidrosis. The cause was an infection by *Serratia marcesscens*, a chromogenic bacterium whose pigment is called prodigiosin.

They found prodigiosin derivatives in the patient's sweat. The bright red tripyrrole pigment from *Serratia marcescens*, has also been identified in *Pseudomonas magnesiorubra*, *Vibrio psychroerythrus*, and two Gram-negative rod-shaped mesophilic marine bacteria not members of the genus *Serratia*.[2]

Recently, these tripyrrole molecules have received renewed attention owing to immunosuppressive and anticancer properties reported.[3] The physiology and regulation of prodiginine production in *Serratia* and *Streptomyces* are now well understood, although the biological role of these pigments in the producer organisms remains unclear. However, research into the biology of pigment production will stimulate interest in the bioengineering of strains to synthesize useful prodiginine derivatives.

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Black

There is a wide range of differential diagnoses when dealing with a nail pigmentation.[1] The clinical features and the history should help in differentiating melanocytic activation, melanocytic proliferation and other causes (hemorrhages...). In this case both pregnancy and medications may be responsible for the brown-black pigmentation of the nails by melanocytic activation. This case report is very interesting for both: the authors "process to make the diagnosis, the first description of tinzaparin as a cause of nail pigmentation".

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Chromonychia

Véronique BLATIÈRE

Table 1: Diagnostic criteria for Kawasaki disease by Han R.K et al.[1]

Diagnostic criteria for Kawasaki disease	
Fever	at least 5 day duration (high, spiking, not responsive to antimicrobial or antipyretic agents)
Presence of at least 4 of the following principal clinical features*	
Polymorphous exanthem	involving face, trunk, extremities, perineal region
Bilateral conjunctivitis	non exudative, bulbar more than palpebral or tarsal
Changes in the lips and oral cavity	dry cracked lips, "strawberry tongue," erythema of oropharynx
Changes in extremities	erythema of palms and soles, edema of hands and feet, followed 1–3 weeks later by desquamation of fingers, toes and in infants, perineal region)
Cervical lymphadenopathy	> 1.5 cm in diameter, usually firm, slightly tender
Exclusion of other diseases with similar findings	

*A typical Kawasaki disease may be diagnosed in patients with fever who have fewer than 4 of the principal features if they have coronary artery changes noted on 2-dimensional echocardiography.

Table 2: Treatment of Kawasaki disease

Treatment of Kawasaki disease (1)	
Intravenous gamma globulin (IVGG)	2 g/kg as single infusion over 12 hours; should be given within 10 days of onset of fever
Acetylsalicylic acid (ASA)	80-100 mg/kg per day, divided into 4 doses, until patient is afebrile then 3-5 mg/kg every day for 6-8 weeks

Table 3: Nail symptoms in Kawasaki disease

Nail symptoms in Kawasaki disease	Time of onset
Transverse orange-brown chromonychia	5th and 8th day of fever onset
Leuconychia partialis	2 weeks after the onset of symptoms
Periungual desquamation	2nd to 3rd week
Transverse leuconychia (Beau's lines)	1 or 2 months (sometimes replace the orange-brown chromonychia)
Onychomadesis	1 week after periungual desquamation
Nail bed fissuring	1 or 2 months
Onycholysis	1 or 2 months
Nail degloving	1 or 2 months
Pincer nail deformity (spontaneously resolving)	1 or 2 months

Osvaldo CORREIA

Melanoma & drug induced disorders

MELANOMA

Fanti PA, Dika E, Misciali C, Vaccari S, Barisani A, Piraccini BM, Cavrin G, Maibach HI, A. Patrizi A. Nail apparatus melanoma: Is trauma a coincidence? Is this peculiar tumor a real acral melanoma? Cutan Ocul Toxicol 2013; 32(2): 150-153.

Nail Apparatus Melanoma (NAM) is rare, particularly in Caucasians. The etiology, pathogenesis and natural history remain poorly understood. This study investigates the potential risk factors of nail melanoma, emphasizing trauma and UV exposure. Out of 1170 melanomas diagnosed from January 1995 until June 2011, 34 patients were affected by NAM (2.9%). Two deceased patients with insufficient medical records and one woman with a personal history of breast cancer were excluded. 31 cases entered in this study: 21 were women (67.7%) and 10 men (32.3%). The mean age at diagnosis was 64.3 (29-88 years). Most NAMs were localized on the thumb (45.2%) and on the great toe (25.8%). In 64.5% of the patients, personal history was positive for an acute or chronic trauma of the nail apparatus; the thumb and the great toes were the most affected. The authors also investigated the presence of UV changes in the nail bed and matrix and they observed the presence of solar elastosis in the nail bed in 4 out of 21 patients. No infections were referred from medical history. Patients survival was better on fingernails. The authors conclude that NAM is a distinct melanoma with its own pathogenesis and prognostic criteria.

Lesage C, Journet-Tollhupp J, Bernard P, Grange F. Post-traumatic acral melanoma: An underestimated reality? Ann Dermatol Venereol 2012; 139: 727-731.

The authors reported a case of a man aged 73 with acral melanoma in which a trauma seems implicated in the progression of a tumour. The examination revealed a dystrophic and hyperkeratotic nail destroyed by a growing lesion on his right big toe. Histological study showed an ulcerated superficial spreading melanoma with a Breslow thickness of 4 mm. Sentinel node was negative.Treatment was amputation. This toe had been fractured when the patient was 20 years old, with subsequent progressive nail dystrophy. The altered nail was submitted to regular trauma with even occasional nail avulsion.

Miranda BH, Haughton DN, Fahmy FS. Subungual melanoma: An important tip. J Plast Reconstr Aesth Surg 2012; 65:1422e-1424

In this paper, the authors described a 34-year old healthy female, who presented with a 3-year history of brown discolouration of the right index fingernail. She presented with nail discolouration that began as a longitudinal pigmented band, but had progressed to almost total melanonychia. The authors claimed that the clinical appearance was highly suspicious of Hutchinson's sign for subungual malignant melanoma. After nail removal an incisional biopsy of the nail matrix was performed. The histology showed hyperkeratotic stratified squamous epithelium, with no evidence of malignancy. Due to a high index of clinical suspicion, three further biopsies were carried out: two from the lateral aspects of the nail bed and matrix and one from a less deeply pigmented area of the finger tip. The histology of the lateral biopsies indicated no increase in abnormal melanocytes. However the biopsy from the less deeply pigmented area, distal to the nail matrix, indicated an increase in abnormal melanocytes, keeping with acral lentiginous melanoma *in situ*. The patient subsequently underwent amputation of the index finger at the level of the middle phalanx.With this case the authors want to emphasize that even biopsy of the most deeply pigmented areas of the nail matrix can give false negative results, hence increasing the risk of diagnostic delay or misdiagnosis.

COMMENTARY O. CORREIA

Nail Apparatus Melanoma (NAM) is rare, particularly in Caucasians.[1] NAM accounts for 1.4% of all cutaneous melanoma (CM) in England and 2.8% in Scotland. Sydney Melanoma Unit reports only 0.31% of NAM. There is no clear epidemiologic association with race, skin type or sun exposure, though the incidence of NAM to CM in non-Caucasians is much higher. Up to 23% of melanomas in the Japanese, 17% among Hong Kong Chinese and 25% in Afro-Americans are located at the nail apparatus. Out of 1170 melanomas, mentioned in the Fanti et al paper from Italy, 34 patients had NAM (2.9%). Nail

Melanoma & drug induced disorders

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melanoma appears to be a peculiar clinical entity, with distinct characteristics if compared with melanoma in other places. Little is reported about NAM pathogenesis, except traumatic injuries as a causal factor. UV exposure is debated in nail melanoma because of its structure. The study of Fanti et al investigates the potential risk factors of NAM, namely trauma and UV exposure.

Trauma appeared as the most reported event preceding melanoma in this location.[1-6] The risk is multiplied for repeated trauma, suggesting a "dose-effect" relationship. The main affected digits are the thumb and hallux, as they are the most exposed to trauma. In the literature, a history of trauma was found to be very variable (8.7 to 39.5% depending on the series).[1-6] Only 9% of patients of the retrospective series of Kaskel et al reported a probable association between trauma and melanoma.[5] However in the study of Fanti et al[1] a history of trauma was recorded in 64.5% and trauma seems to be evident in the case reported by Lesage et al.[6]

A recent study referred to trauma as a factor influencing prognosis in melanoma[7] stating that trauma is more associated with nodular NAM and poor prognosis. Unlike cutaneous melanoma, UV exposure does not seem to play a relevant role in NAM, because the nail plate is too dense for significant light penetration. However Fanti et al[1] found solar elastosis in the nail bed in 4 out of 21 patients. In the clinical case reported by Miranda et al[8], the clinical aspect was highly suspicious for subungual malignant melanoma with Hutchinson's sign. However, the nail matrix histology had no evidence of malignancy. Further biopsies only showed abnormal melanocytes consistent with acral lentiginous melanoma *in situ* on a less deeply pigmented area of the finger tip.

NAM usually appears as an irregular melanonychia, but in 20% of subungual malignant melanomas they present with amelanocytic lesions, rather than melanonychia.[9] The overall reported 5 year survival rate of acral lentiginous melanoma is poor, in comparison to other histological subtypes, being as high as 25 to 51%.[10] This poor prognosis has been attributed to delay in diagnosis. Early diagnosis is crucial in melanoma, including NAM. An ABCDEF mnemonic was created by Levit et al[11] for early detection of NAM. All dermatologists should keep it in mind:

"A": stands for the age of the patient at presentation. Subungual melanoma most commonly occurs between 50 and 70 years of age, although it has been reported to occur in patients as young as 1 and as old as 90.

"B": stands for borders - which represent the most common clinical presentation of a subungual melanoma with a pigmented band composed of variegated shades of brown-to-black with a breadth of over 3 mm and irregular or blurred borders **(Fig 1)**.

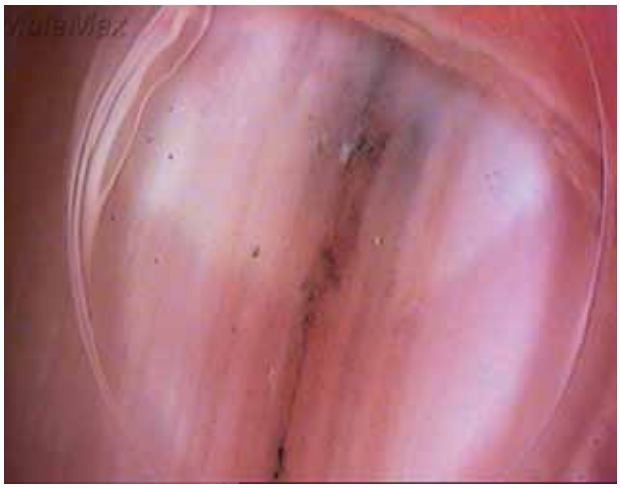

Fig1 - Right thumbnail longitudinal pigmentation. Dermatoscopy: brown longitudinal lines irregular in their width, spacing and colour.

"C": stands for change - a sudden, recent, or rapid increase in the size of the pigmented band, comparable to the radial growth phase, or a change in nail plate morphology.

"D": stands for the digit most commonly involved; usually single digit involvement particularly the thumb, then the great toe or the index finger being most commonly involved.

"E ": stands for extension of the pigment onto the proximal and/or lateral nailfold (i.e., Hutchinson's sign).

"F ": stands for family or personal history of melanoma and/or dysplastic nevus syndrome.

Early diagnosis of NAM is essential, ideally at the in situ stage (NAMis). Dermoscopy is very important [12] and intraoperative dermatoscopy with patterns of longitudinal melanonychia of bed and nail matrix have been described.[13]

More recently perioperative confocal microscopy of the nail matrix has been used in the management of in situ or minimally invasive subungual melanoma.[14] A conservative and functional surgical management of *in situ* or minimally invasive subungual melanoma has been proposed by Haneke et al.[15] Recent papers confirm this conservative treatment with non-amputative wide excision of the nail unit, followed by a skin graft,[16,17] as a good cosmetic and functional approach with excellent oncologic safety **(Figs 1-5)**. However, long-term follow-up is mandatory in order to look for recurrences that can appear a long time after treatment.[17]

Conservative surgical management of subungual melanoma as described by: Duarte AF, Correia O, Barros AM, Azevedo R, Haneke E. Nail matrix melanoma *in situ*: conservative surgical management. Dermatology 2010; 220:173-5

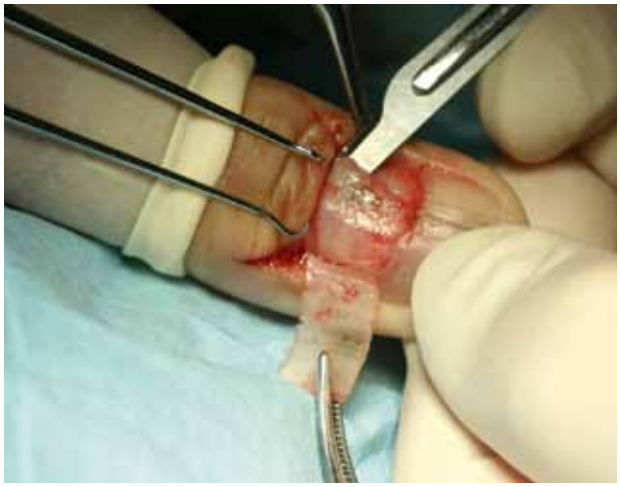

Fig2 - Excisional tangential nail matrix biopsy. © O. Correia

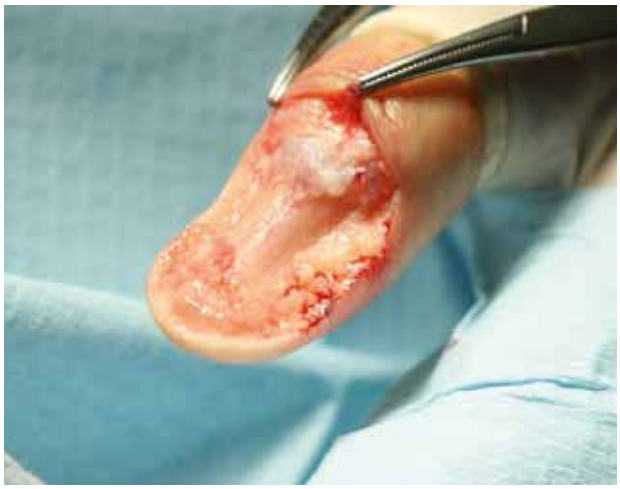

Fig3 - Total removal of the nail unit. © O. Correia

Fig4 - Reconstruction of the finger using a full-thickness skin graft taken from the right arm. © O. Correia

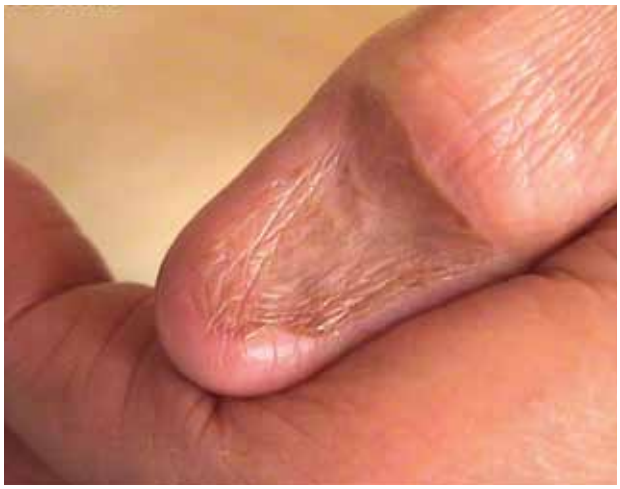

Fig5 - Clinical aspect at 1-year follow-up. © O. Correia

Melanoma & drug induced disorders

Osvaldo CORREIA

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DRUG INDUCED DISORDERS

Fenniche S, Hammami H, Badri T, Mokhtar I, Benmously R. Subungueal haemorrhages following docetaxel (taxotere) treatment. Curr Drug Saf 2012; 7:247-249.

An 80-year-old man with prostate adenocarcinoma was treated 3-weekly with docetaxel. Nail changes occurred after the 5th cycle of docetaxel. On examination they found orange discoloration of the nail plates, subungual haemorrhages and onycholysis involving nails of all the digits and toenails of both hands and feet. These features were highly suggestive of nail toxicity following docetaxel therapy.

Kwon SH, Choi JW, Hong JS, Byun SY, Park KC, Youn SW, Huh CH, Na JI. Gefitinib-Induced Paronychia: Response to Autologous Platelet-Rich Plasma. Arch Dermatol 2012; 148: 1399-1402.

A 68-year-old woman with lung adenocarcinoma and multiple bone and brain metastases was initiated with gefitinib therapy at an oral dose of 250 mg/d, after 4 months of inefficient chemotherapy with gemcitabine and cisplatin. One month later, multiple paronychia with periungual granulation tissue appeared on the nailfolds of the first, second, and third toenails of both feet. This paronychia recurred repeatedly despite the use of topical corticosteroid and topical and systemic antibiotics for more than a year. She then began daily topical autologous Platelet-Rich Plasma (PRP) treatment. After 3 months, the lesion showed marked improvement with minimal pain or discharge. However gefitinib therapy was discontinued owing to the poor response of the tumor to this drug.

Melanoma & drug induced disorders

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Peuvrel L, Quéreux G, Brocard A, Saint-Jean M, Dréno B. Onychopathy induced by temsirolimus, a mammalian target of rapamycin inhibitor. Dermatology 2012; 224:204-8.

The authors reported 2 female patients aged 51 and 83, both with metastatic renal cell carcinoma which developed after 6-7 months with temsirolimus (25 mg IV, weekly), a dystrophy of the 20 nails consisting of nail fragility, distal onycholysis, yellow discoloration and associated in one case with painful paronychia. Topical steroids improved the paronychia, without changing the nail dystrophy. The authors also review published data on cutaneous, mucosal and nail toxicities induced by temsirolimus and everolimus, two mTOR (mammalian target of rapamycin inhibitors). These targeted therapies are used as anticancer agents, and their parent molecule sirolimus is indicated to prevent organ rejection after transplantation.

COMMENTARY O. CORREIA

Docetaxel belongs to the taxane group of chemotherapeutic agents and is used in the management of various malignant diseases. Nail changes have been reported in up to 44% of the patients treated with docetaxel, including nail bed dyschromia, onycholysis **(Fig 6)**, red or orange Beau's lines, pyogenic granulomas, subungueal hyperkeratosis and subungueal haemorrhages.[1,2,3]

Gefitinib inhibits tyrosine kinase activity of epidermal growth factor receptor. This class of drugs has been recently used to treat lung, pancreatic, gastric, colorectal, head and neck carcinomas. Papulopustular eruption (in up to 85% of patients), xerosis, hair abnormalities, pruritus, and nail alterations (paronychia, periungual pyogenic granuloma-like lesions, onycholysis and other kinds of onychodystrophy) have been reported.[4] Kwon SH et al[5] reported improvement of gefitinib-induced paronychia by daily topical autologous platelet-rich plasma (PRP). Compared with invasive treatments or systemic antibiotic therapy, PRP may be an interesting treatment modality for long-term and maintenance therapy in those patients taking gefitinib or similar for months to years. However these data must be confirmed in longer and larger studies.

Temsirolimus and everolimus are a recent class of anticancer agents (used in different cancers, such as advanced renal cell carcinoma, neuroendocrine pancreatic cancer and have also been used in the prevention of organ rejection after transplantation) that can induce nail disorders in 5-14% of the patients.[6]

Patients must be advised of these kinds of adverse nail effects. Dermatologists and general practitioners should be alerted and receive appropriate clinical guidance to avoid unnecessary tests and treatments, which are sometimes suggested by uninformed podiatrists or non-medical people.

Fig6 - Onycholysis and Beau's lines in a patient treated with docetaxel for breast cancer. © O. Correia

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David DE BERKER

Treatment of nail psoriasis

Saraceno R, Pietroleonardo L, Mazzotta A, Zangrilli A, Bianchi L, Chimenti S. TNF-alpha antagonists and nail psoriasis: an open, 24-week, prospective cohort study in adult patients with psoriasis. Expert Opin Biol Ther. 2012 Nov 16. [Epub ahead of print] PubMed PMID: 23157654.

72 patients with nail psoriasis were recruited to an open label 24-week prospective study in which they were allocated to treatment with adalimimab, infliximab or etanercept. Nail psoriasis severity was assessed by NAPSI at baseline, at weeks 14 and 24. A NAPSI of greater than 15 was an inclusion requirement and mycological infection and other nail treatments exclusions. Patients were monitored consistent with the guidelines for the drugs. Due to drop outs and infection, only 60 patients were evaluated. The authors noted a more rapid response in those treated with infliximab and a greater level of overall nail improvement at 24 weeks with this drug in comparison with the other.[2]
The figures were:

	Week 0	Week 14	Week 24	p
Adalimumab	33.1 (+/-14.9)	21 (+/-8.91)	11.4 (+/-4.6)	<0.0002
Etanercept	34.8 (+/-12.4)	23.6 (+/-10.4)	10.6 (+/-5.2)	<0.0016
Infliximab	33.3 (+/-9.8)	14.9 (+/-4.2)	3.1 (+/-3.3)	<0.00001

At week 14 efficacy was greater in the infliximab group than with the other 2 treatments ($p<0.05$). The standard deviations on the distributions suggests that more patients are clear of nail psoriasis if treated with infliximab than those treated with adalimimab or etanercept and this was not stated in the report.

Jemec GB, Ibler KS. Treatment of nail psoriasis with TNF-alpha or IL12/23 inhibitors. J Drugs Dermatol. 2012; 11:939-42.

Is there a Biologic of choice for people with nail psoriasis? This review aims to help us answer this question. The authors sought all randomized controlled trials for adalimumab, alefacept, briakinumab, etanercept, golimumab, infliximab and ustekinumab where fingernail assessments were made.
The RCT for adalimumab, with 81 patients and standard dosing against placebo, showed a 50% improvement compared with 8% in the placebo group at 16 weeks ($p=0.048$). Improvements were greater in open trials and over longer periods, but such trials were subject to a range of loose ends.
Briakinumab is an antibody directed against the p40 subunit of interleukins 12 and 23.
317 people were randomized to the drug or methotrexate in a protocol driven dose between 5 and 25mg. Mean scores for the target fingernail at baseline, week 24, and week 52 were 4.8, 2.1, and 1.2, respectively in the briakinumab group, as compared with 4.8, 3.0, and 3.0, respectively in the methotrexate group ($p<0.001$ for the change from baseline with briakinumab vs. methotrexate).
An RCT with etanercept was randomized between 2 common etanercept protocols, so there was no blinding or placebo. The pooled result for NAPSI improvement was a drop in the target nail from 4.64 to 2.38 over 54 weeks ($p<0.001$). Golimumab data reports an RCT where nail data is available on 287 people, divided between placebo and doses of 50mg or 100mg of drug every 4th week. On the latter dose, people had a drop in their target nail NAPSI of 43% (week 14) and 54% (week24). There is much data on infliximab, part open trial and some RCT. With the RCT, randomization was between a routine dosing and placebo on 378 patients. Target nail scores were used, but only percentage changes reported. Statistics were undertaken on percentages creating anomalous standard deviations and results of a 31.9% difference between placebo and drug at 10 weeks increasing to 59.5% at 24 weeks ($p<0.0001$).
There were no RCTs for ustekinumab reporting nail disease so a small open trial is cited where 27 patients demonstrated a change of median NAPSI from 73 to 37 at 16 weeks and 0 at 40.

Treatment of nail psoriasis

David DE BERKER

Fischer-Levancini C, Sánchez-Regaña M, Llambí F, Collgros H, Expósito-Serrano V, Umbert-Millet P. Nail psoriasis: treatment with tazarotene 0.1% hydrophilic ointment. Actas Dermosifiliogr. 2012 Oct;103(8):725-8. Epub 2012 Jul 19. English, Spanish. PubMed PMID: 22818395.

In this open trial of 6 patients with nail psoriasis, the disease was scored using the NAPSI. No patients were on systemic therapy at the time. Baseline photographs were taken at 0, 3 and 6 months. Treatment was applied as ointment under tape at night. Over 6 months, there was a drop in the NAPSI from a mean of 14.3 to 2.33 (p=0.007). Subungual hyperkeratosis is reported as a separate feature that also reduced substantially in that period. No adverse effects were noted.

De Simone C, Maiorino A, Tassone F, D'Agostino M, Caldarola G. Tacrolimus 0.1% ointment in nail psoriasis: a randomized controlled open-label study. J Eur Acad Dermatol Venereol. 2012; 13. doi: 10.1111/j.1468-3083.2012.04642.x. [Epub ahead of print].

In this small trial tacrolimus is assessed and found to be of some value in treating nail psoriasis. Twenty one patients were enrolled. All had bilateral fingernail psoriasis. None had been taking systemic therapy or using topical hand therapy in the previous 3 months. Psoriasis affected at least one fingernail on each hand and there were no nails with clinical features of onychomycosis. Patients were randomized to use tacrolimus 0.1% ointment on the nails of one hand and nothing on the other. They applied the ointment at night with no occlusion for 12 weeks. Assessment was by use of the NAPSI at the outset,then at 6 and 12 weeks by one assessor. The modified NAPSI was also employed for a target nail in each hand and a global scoring scheme comprising, 0=no improvement, 1=mild improvement, 2=moderate improvement and 3=cleared or almost cleared.
One patient withdrew due to paronychia. In assessment of the remaining patients, there was a significant improvement by all measures in the nails or nail (modified NAPSI) of the treated hand. The most obvious change was in the modified NAPSI with a reduction in the treated nail from 13.2(10.7-15.8) to 4.6(2.4-6.7) in comparison with the untreated nail of 12.8(10.4-15.2) to 12.7(10.1-15.4). Complete clearance was seen in 36 of the 90 affected treated nails and in the untreated hand the count of affected nails increased from 81 to 83 during the course of the study.

Nakamura RC, Abreu Ld, Duque-Estrada B, Tamler C, Leverone AP. Comparison of nail lacquer clobetasol efficacy at 0.05%, 1% and 8% in nail psoriasis treatment: prospective, controlled and randomized pilot study. An Bras Dermatol. 2012; 87:203-11.

This was a prospective, controlled randomized study in 15 patients using 3 different strengths of clobetasol (0.05%, 1% and 8%) in a nail lacquer base as treatment for nail psoriasis. There were 5 patients in each group, with each group applying one of the steroid lacquers to the left hand and base coat lacquer to the right hand twice a week for 16 weeks. Clinical evaluation was done by photographic records and the NAPSI score of both treated and control hands, as well as the modified NAPSI score of the most affected nail. Scoring was at baseline and for 4 weekly intervals up to 16 weeks. Patient reported outcome was measured by a questionnaire asking them to report improvement in categories of >50%, 20-50% and <20%. The authors report a "statistically relevant" clinical response judged by whole hand NAPSI and single nail modified NAPSI in the 8% vs control group.

Inclusion criteria comprised presence of bilateral fingernail psoriasis in an adult with no use of topical or systemic treatment throughout the study and 4 weeks prior to it. Mycological microscopy and culture were negative. Response was gauged through difference of the right and left scores and scores of the same nail or hand, before and after. Pooled right left comparison of the modified NAPSI on the worst digit was significant after 16 weeks. Comparison of the left and right hands was not statistically significant, although there was some improvement. No adverse effects were reported and in particular no periungual atrophy or discomfort.
The 3 different concentrations did not reveal any

significant difference of efficacy between them, although the authors say that there was a non-significant trend to a dose response curve, suggesting that a larger sample may have demonstrated increased benefit from more concentrated lacquer. Patient reported outcome was 9 with moderate to excellent response and 6 with unsatisfactory response or not responding to the questionnaire.

Kyriakou A, Patsatsi A, Sotiriadis D. Anti-TNF agents and nail psoriasis: a single-center, retrospective, comparative study. J Dermatolog Treat. 2013; 24: 162-8.

39 psoriatic patients were treated with infliximab[12], adalimumab[14] and etanercept[13]. They were all assessed using PASI and NAPSI at the time of initiation, commencing the biologic for treatment of moderate to severe psoriasis with PASI and NAPSI greater than 10. Inclusion criteria included no systemic treatments in the last 12 weeks and no previous treatment with a biologic agent. Exclusion criteria included the presence of psoriatic arthritis due to the concern that this might act as a confounding factor. PASI and NAPSI were repeated at 12, 24 and 38 weeks throughout the treatment period.
There were slightly more women in each treatment group and subjects were slightly older in the etanercept group. Treatment was with standard licensed doses. The median PASI at outset ranged from 24.3 for adalimumab to 20.9 for etanercept with median NAPSI 69 for etanercept, 69.5 for adalimumab, to 75 for infliximab. After 48 weeks this improved to 5, 7.5 and 4 respectively.

COMMENTARY D. DE BERKER

These papers divide into topical therapies and biologic therapies. With the topical therapy papers a range of questions arise concerning methodology. The gold standard for a topical therapy study is to do a right/left comparison, with randomization between right and left to reduce the effect of different levels of disease in the dominant hand. The number of patients should be large enough to ensure sufficient power e.g. that a 20% difference between the treatment and control will be detected. The studies should then have a placebo element on the control limb and ideally have blinding of the patient and the clinician. Outcome should be scored using a validated technique and with a sufficient follow-up period. Confounding factors, like overlapping other treatments, should be exclusion criteria. All these elements are often difficult to achieve, particularly in small trials that are undertaken in the normal clinical setting as an extension of normal clinic practice.
The papers offer us 3 products; a steroid lacquer, tacrolimus ointment and tazarotene ointment **(Table 1)**.

All 3 offer positive findings with respect to the active treatment. Although the work with clobetsol lacquer had only 5 patients using the 8% strength, the general methodology was of the highest standard amongst the trials and the fact that the positive finding was in the greatest strength of steroid suggests that it is a genuine dose-response observation. Robert Baran and Antonella Tosti reported their experience with 8% clobetasol propionate lacquer in 45 patients and Regana undertook a similar study but with a combination of clobetasol

Table 1

	Clobetasol lacquer 8%	Tacrolimus 0.1% ointment	Tazarotene 0.1% ointment
Right left comparison	Yes	Yes	No
Right left randomization	No	Yes	No
Sufficient numbers	No (n=5 for 8% group)	Yes (n=90)	No (n=6)
Placebo control	Yes	No	No
Patient blinded	Partial	No	No
Clinician (scorer) blinded	Partial	No	No
Validated outcome measure	Yes	Yes	Yes

David DE BERKER

propionate lacquer with tacalcitol cream over 24 weeks [1] and Cantoresi over 9 months.[2] Such periods may be useful to establish a more clear effect.

In the tacrolimus study, the number of patients was much higher, which helps to overcome some shortcomings in methodology. However, it is still important that the control hand did not receive the vehicle emollient, as this can have value in the management of nail psoriasis. The last study has the least data and did not follow established parameters for a clinical trial. All that said, when interested clinicians invest time in trying to answer questions in their own clinics, they often do not have the machinery of drug trial organization to offer and we should look at their findings and think about whether they are the beginning of a good idea **(Fig 1)**.
At present, only the tacrolimus 0.1% could be used in clinics, as the other 2 formulations are not commonly available.

The following three papers look at biologics. The Jemec review paper attempts to answer the question that all those treating patients with severe nail disease would like answered - which of the biologics is best for nails? Some of the agents, such as golimumab and briakinumab, are not generally available yet. All the studies were based on large numbers of patients, but typically used slightly different methodology from each other and none were head to head trials of different biologics. Accordingly, the collection of data is not completely aligned and does not allow us to answer the question above. We are left with the evidence that they all work and that it is not predictable whether one will work better than another for a patient with nail disease **(Fig 2)**.

This slightly non-committal conclusion differs from that drawn by the authors of the other two papers. The first by Saraceno et al is close to a head to head with 3 of the main biologics, but it is retrospective and there is no mention of how patients were randomized to the different drugs and also what pattern of arthritis was found in those affected. This could have relevance as we know that distal interphalangeal joint arthritis complicates and possibly drives the adjacent nail psoriasis **(Fig 3)**. Nevertheless, the study appears to show that infliximab works somewhat quicker and achieves greater clearance of nail disease than the other 2 biologics. Kyriakou et al make the

Fig1 - Local hand and nail care measures are important. In this instance the nails are too long and will lead to catching the free edge with upward leverage. The nail will also reduce access of topical therapies to the nail bed to treat distal nail bed diseases. © D. De Berker

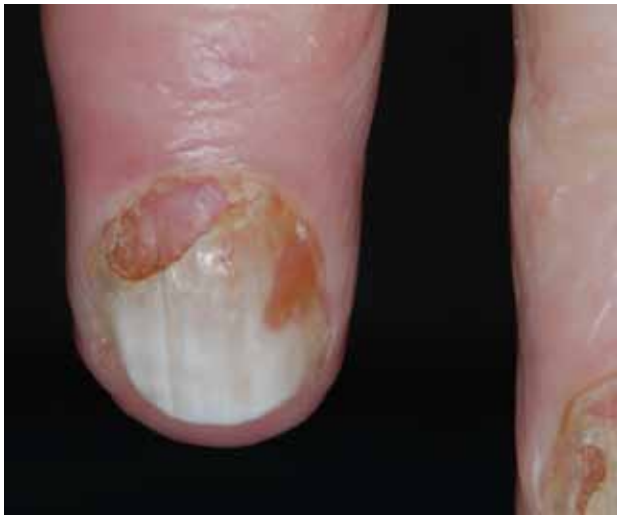

Fig2 - There are instances of paradoxical psoriasis, with nail disease arising in people being treated with anti-TNF alpha agents for arthritis where previously there was no skin or nail disease. © D. De Berker

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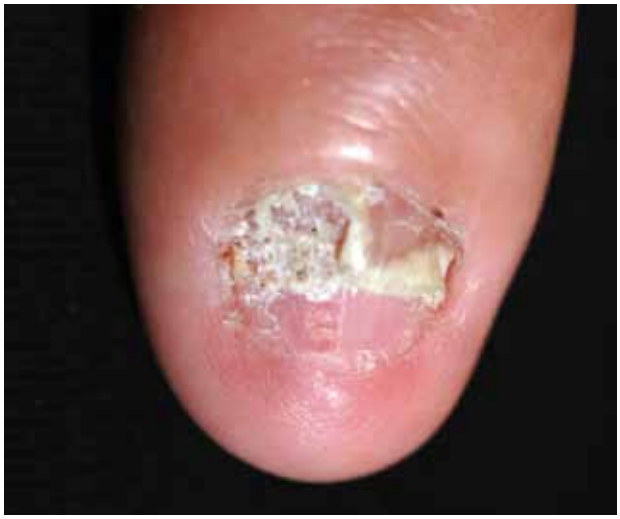

Fig3 - Psoriatic arthritis of the distal interphalangeal joint increases the likelihood of severe nail dystrophy of that digit. © D. De Berker

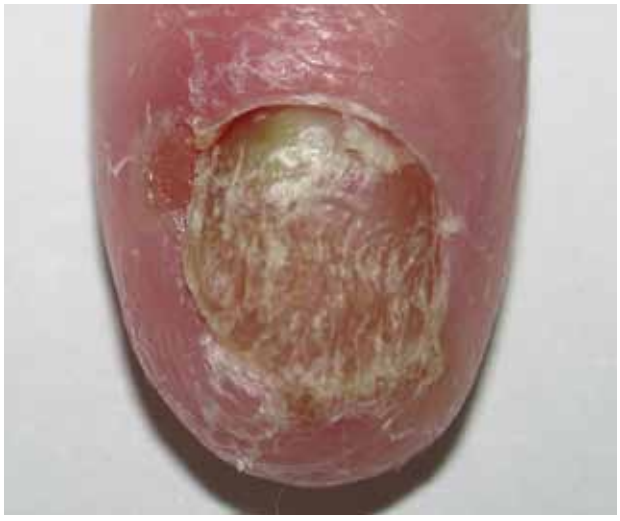

Fig4 - Pustular nail disease remains a challenge in the face of all systemic therapies, including the Biologics. © D. De Berker

same observation, although interpretation of the results is made more difficult by the use of percentages throughout. Hence the percentage changes are compared and all the statistics are done in comparison with baseline for each drug. All three show very significant changes in the NAPSI at each of the assessment intervals in comparison with baseline, but we are not making comparisons between the drugs. From this data, it looks as if infliximab is slightly ahead of etanercept which is slightly ahead of adalimumab. So whilst a formal evidence review does not conclude that there is a clear difference between biologic agents with respect to nail disease, small retrospective studies raise the possibility that infliximab may be more effective. The other question we need to address is what works best for pustular nail psoriasis and this will always be based on small numbers of patients **(Fig 4)**.

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Bruno FOUILLOUX

Lasers & onychomycosis

Kimura U, Takeuchi K, Kinoshita A, Takamori K, Hiruma M, Suga Y. Treating onychomycosis of the toenail: clinical efficacy of the sub-millisecond 1,064 nm Nd: YAG laser using a 5 mm spot diameter. J Drugs Dermatol. 2012; 11:496-504.

The efficacy of oral antifungal treatment ranges from 14% to 50% with a recurrence (relapse or reinfection) rate of 14 to 53%. The use of phototherapy for treating onychomycosis was first reported in literature in 1976 with the use of a carbon dioxide (CO2) laser. However, the energy of the CO^2 laser was only slightly absorbed beneath the skin surface, making it less effective for treating subungual mycotic infections. The N2 laser was then evaluated, but the energy output was not sufficient to treat infection in the deeper layers.

In this study, the authors evaluated the preliminary data concerning the safety and the efficacy of the sub millisecond Nd:Yag 1,064 nm laser in the treatment of onychomycosis with a 16 weeks follow-up average, after the final treatment. The study was based on thirteen patients (9 females, 4 males) with an average age of 68 years. 37 toenails were selected.

The Nd:Yag laser was used with a 5 mm spot diameter, with the energy fluence set at 14J per cm^2 , an exposure time per pulse of 300µs and a repetition rate of 5 Hz. Each infected toenail was treated in a criss-cross pattern with two alternating passes (one vertically and one horizontally) of laser pulses to cover the full nail surface. **(Figs 1 & 2)**.

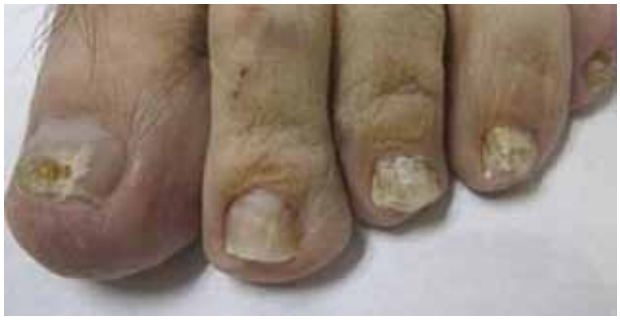

Fig1 - Before treatment. © B. Fouilloux

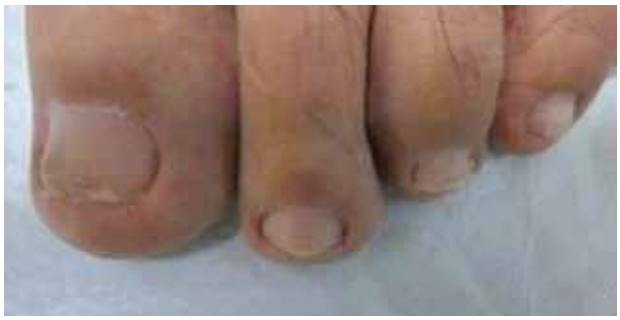

Fig2 - During treatment. © B. Fouilloux

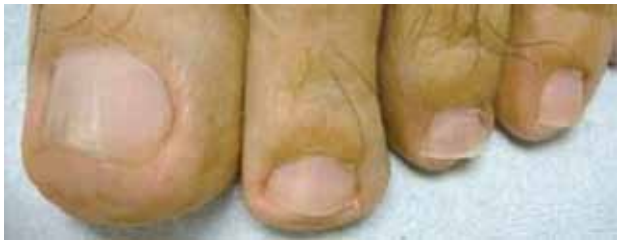

Fig3 - After treatment. © B. Fouilloux

Seven subjects were treated three times, five subjects were treated twice, and one patient was treated once. Treatments were performed 4 and/or 8 weeks apart **(Fig 3)**.
Of the 37 infected toenails treated, 30 (81%) showed either complete clearance or "moderate" clearance. 51 % of the toenails had complete clearance (clinical appearance of clear nail confirmed by negative direct microscopy examination). The great toenail constituted only 26% of all with complete clearance. The benefit of a bigger spot size, such as that experienced in this study, is that the treatment time is shorter than with a small spot size.
The effectiveness of laser is thought to result from bulk heating of the thick, horny cell layer as well as the internal nail harbouring the fungus. Particular features of the laser wavelength or the heating effects may stimulate infected nails to grow more rapidly.
In conclusion, the sub-millisecond 1,064 nm Nd :Yag laser is a safe and effective treatment modality for onychomycosis. The clinical efficacy and significance of this novel treatment for management of onychomycosis should be further evaluated in broader patient populations.

Lasers & onychomycosis

Bruno FOUILLOUX

Gupta AK, Simpson F. Newly approved laser systems for onychomycosis. J Am Podiatr Med Assoc. 2012;102: 428-30. In January 2012, four laser-based systems were approved by the US Food and Drug Administration (FDA). The laser therapies approved for onychomycosis treatment are all Nd:YAG 1064 lasers.

The first device approved was the PinPointeFootLaser in the US, Canada, the European Union and Australia. A single clinical study has been released for this laser which shows an improvement in 79% (11/14) of the toenails after 6 months of treatment.
The CuteraGenesisPlus laser has the same technical specifications, but there is no data available from any clinical trials. A white paper published on the GenesisPlus model showed 70% improvement with a clear nail in seven patients after two laser treatments.
The CoolTouch VARIA model is unique in the category of short-pulse lasers, because it is operated together with a cryogen cooling system. It may be advantageous to ensure patient comfort during treatment.
The Light Age Q-Clear laser is the only Q-switched nanosecond laser that has been approved for the cosmesis of onychomycosis.
It should be noted that FDA-approved laser therapies for onychomycosis have not yet undergone double-blind randomized clinical trials as have drug therapies such as terbinafine and itraconazole. It is hoped that laser manufacturers will carry out full clinical trials, in order to fully substantiate the promise of laser treatment.

Ledon JA, Savas J, Franca K, Chacon A, Nouri K. Laser and light therapy for onychomycosis: a systematic review. Lasers Med Sci. 2012 Nov 20.Epub ahead of print.

Lasers have been suggested for the treatment of onychomycosis because of their minimally invasive nature and because they only require a few treatment sessions.
The carbon dioxide (CO2) laser system is the oldest of the laser therapies used for onychomycosis. It is ablative in nature and can serve as primary treatment or as an adjunct to a topical antifungal, providing a mean of penetration through the nail plate.
Complete clearance with no recurrence was reported in 75% of the cases after a 3 year follow-up period.
The observation that UV light is extremely germicidal has led researchers to investigate possible therapeutic applications of UV light to treat onychomycosis. Despite the fact that UVA and UVB light have not been shown to penetrate nail plates, the mutagenic potential of UV light has limited its use in the treatment of onychomycosis and has encouraged exploration of other, potentially safer, therapeutics.

Photodynamic therapy (PDT) is the most studied light therapy for onychomycosis. ALA is the gold standard in porphyrin sensitizers. The only clinical trial evaluating PDT for treatment of onychomycosis was carried out after chemical avulsion of the toenail. After three sessions the authors reported a 43,3% clinical and mycological cure rate at 12 month follow-up.
PDT without chemical avulsion has also been reported. A successful resolution was also reported in an onychomycosis caused by non dermatophyte molds.
Several investigations into the effects of PDT with certain synthetic photosensitizers have been conducted with promising in vitro results.
Sylsens B was considered as one of the more effective synthetic photosensitizers. It was found to penetrate only *T.rubrum*-infected human skin, not healthy skin. With UVA light, the addition of Sylsens B produced similar efficacy with lower UVA energies.
Toluidine Blue O (TBO) has also been studied with red light in eradication of *T.rubrum*. The combination of the two devices resulted in total inhibition of growth with 72J/cm^2 total irradiation.

Bruno FOUILLOUX

Borstein used a dual wavelength 870/930 nm laser and found that 4,074 J/cm² of 870/930 nm resulted in 100% eradication of bacteria, fungi and yeast. After four sessions of 870/930 nm laser followed by 930 nm alone, he obtained clear nail growth in four out of seven patients after 60 days and all the nail cultures were negative.
Landsman confirmed the efficacy of this laser with negative culture and microscopy examination in 38% of patients at a 9 month follow-up.

It is suspected that, thanks to its longer wavelength, Neodyminium-doped yttrium aluminium garnet laser (1,064 nm and 1,444 nm) is able to penetrate more deeply and efficiently targeted fungal overgrowth in the nail bed.
Choi showed a 76% reduction in colony-forming units with a total of 300 J. Colony forming units were reduced by 85,5% with 450 J. Unfortunately, the ventral surface of the toenail maintained signs of infection.
Hochman and Kimura had more promising results with 1,064 Nd:YAG laser with 87,5% of patients having negative cultures after the final treatment.
There is only one study using the femtosecond infrared titanium sapphire laser (800 nm) which shows that in vitro fungal growth can be completely inhibited without affecting the structure of the nail plate.

These relatively non invasive devices are interesting to establish competition with systemic treatments in onychomycosis or to improve them. Some lasers, like the CO_2 870/930 nm dual wavelength and 1064 nm Nd:YAG, as well as PDT have demonstrated some clinical successes,

- yet randomised controlled trials are needed to validate this finding. Many others systems have been evaluated in vivo and ex vivo giving insight into possible future therapies.
- it has been demonstrated that CO2 laser provides better penetration of topical antifungal agents into the nail bed.
- although in vitro studies of the Nd:YAG laser system have yielded conflicting results, clinical studies have shown some promise.
- for PDT, several studies have explored its potential with specific photosensitizers in the eradication of onychomycosis-causing organisms. The majority of this research is in the preclinical stages and is not ready for clinical use today.

Choi MJ, Zheng Z, Goo B, Cho SB. Antifungal effects of a 1444-nm neodymium:Yttrium-aluminum-garnet laser on onychomycosis: a pilot study. J Dermatolog Treat. 2012 Sep 19. [Epub ahead of print].

In this study, the authors investigated the antifungal activities of 1444-nm Nd:YAG lasers in the treatment of onychomycosis by microbiologic analysis and scanning electron microscopy. This testing was based on the scraped toenails of 20 participants, which were prepared on two plastic weighing dishes. One dish was untreated, and the other dish was treated with two different total energies: either 300 J (n = 10), or 450 J (n = 10). Then the effects of the laser were analysed by fungus culture or a scanning electron microscope.
By fungus culture: after treatment, the scraped toenails, treated or not, in each dish were transferred to Sabouraud's liquid medium and incubated at 37°8 for 24 hours. After 5 days of incubation, the colony forming units (CFUs) were counted and divided by the amount of scraped nails.
By scanning electron microscope: the extracted toenail was longitudinally cut in half. One half was treated and the other was not. The nail specimens were then fixed and observed with 100- 20 000x magnification.
Mycological evaluation showed that the number of CFUs in toenails treated with the 1444-nm laser with total energies of 300 J and 450 J was significantly reduced compared to the controls, but there was no significant difference between the laser settings of 300 J and 450 J in the CFU reduction rates.
Scanning electron microscope examinations demonstrated that the 1444 nm Nd:YAG laser causes remarkable morphologic changes to the fungal spores of the lower portions of the toenail. The upper portion of the nail plate, which was more affected by the stronger laser fluencies than the lower portion, showed greatly disintegrated structures of both fungus and toenail.
These data suggest that a Nd:YAG laser with a wavelength of 1444 nm can be used to obtain antifungal effects against onychomycosis. However, to minimize the danger of excessive photodermal effects on human tissues and maximize the antifungal effects of the 1444 nm Nd:YAG lasers, further investigations should be carried out.

Lasers & onychomycosis

Bruno FOUILLOUX

COMMENTARY B. FOUILLOUX

The first data regarding lasers in the treatment of onychomycosis were provided in 2010.

Though a recent in vitro study of Nd:YAG laser on *Trichophyton rubrum* failed to show an inhibition of fungal growth, the authors nevertheless think there is an in vivo efficacy.[1]

In his article, Hees has tried Nd:YAG Q switched laser by varying the wavelength, the fluence, the spot size and the pulse duration. There was no inhibition of fungal growth in any of the treated plates. The differences in size between treated and untreated colonies were not significant.

Zhang et al.[2] shows the efficacy of long pulse Nd:YAG 1064 nm laser on 154 nails of 33 patients divided into two groups. One group was treated by eight sessions with a one-week interval and the second group was treated by four sessions with a one-week interval. The effective rates varied from 51 % to 68 %. There was no significant difference between the groups.

If the use of laser is promising, the studies are inconclusive. They have been carried out on very few patients without any comparison to medical treatment and a very short follow-up of patients (rarely more of 12 months).

The choice of the FDA for Nd:AG 1064 nm long pulse may be explained because it has one of the best penetration levels in tissues available today. However, a photodermic effect, inevitable with a temperature able to destroy fungus, induces heat which is not easily bearable. We can vary the spot size or add a cooling system. Laser therapy cannot be used for onychomycosis with matrix involvement because of the risk of permanent damage to this fragile tissue. It could serve as a substitute for local treatment or to help this one or in patients with severe contraindications to systemic antifungal drugs.

We can hope that, during the next few years, more studies will be carried out about the effect of laser on fungal agents and that they will be performed with clear assay procedure, especially concerning the number of required treatment sessions, on the need or not to thin the thickness of the nail plate beforehand and on the delay between sessions.

Gupta[3] has noted that device-based therapeutic options for onychomycosis are expanding more rapidly than pharmacotherapy. Systemic azoles are the only class of drugs that have shown comparable efficacy to systemic terbinafine, which remains the gold standard. There are now many new topical drugs like tavaborole, efinaconazole and luliconazole. Moreover photodynamic therapy, iontophoresis and laser therapy have shown positive initial results.

In conclusion we can hope that lasers will be used in the near future in the treatment of onychomycosis, especially on the elderly or on patients with many systemic therapies. However, randomized controlled trials would be useful to determine the long-term success of these devices.

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Tumours & nail surgery

Weedon D, van Deurse M, Rosendahl C. "Occult" melanocytes in nail matrix melanoma. Am J Dermatopathol 2012; 34:855.

Melanocytes in the nail matrix can be difficult to detect. The distinction between a melanotic macule and an early ungual melanoma may be impossible. A tiny biopsy from the advancing edge of an early melanoma cannot be diagnosed with certainty **(Figs 1a,b)**. As the melanocytes are difficult to see among the keratinocytes and their morphology is unclear, terms like "acral atypical melanocytic hyperplasia" have been coined. The authors therefore recommend to perform immunohistochemistry staining(s) not only to detect melanocytes, but also to determine their morphology and distribution. Melan A, MART-1 or HMB45, as well as some newer cocktails with a red chromogen, highlight the melanocytes. In early melanoma, the dendrites are longer and plumper than those of normal melanocytes, the nuclei larger and hyperchromatic. Pagetoid spread is easily seen. Inflammatory cells under the lesion are more likely to be the sign of a melanoma than of a melanotic macule. The center of subungual melanoma is usually more diagnosed. The authors conclude their short letter with the words: "Dermatopathology of the nail matrix is not for the faint-hearted or inexperienced."

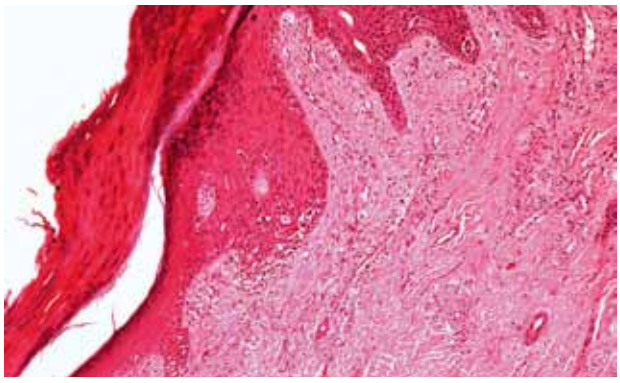

Fig1a - Margin of a subungual melanoma *in situ*, distal nail bed bordering the hyponychium. © E. Haneke

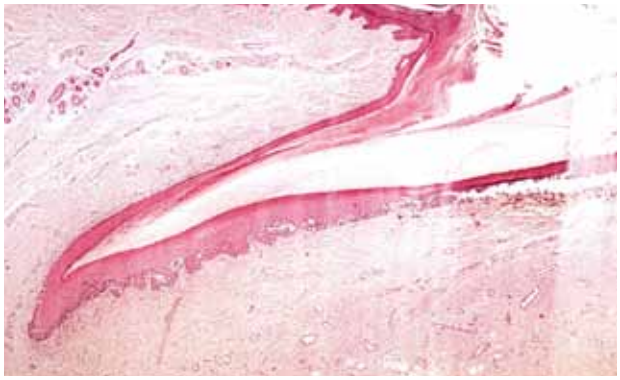

Fig1b - Subungual melanoma *in situ* with easily visible nests of melanoma cells. © E. Haneke

Perrin C, Kettani S, Ambrosetti D, Apard T, Raimbeau G, Michiels JF. "Onycholemmal carcinoma." An unusual case with apocrine and sebaceous differentiation. Are these tumors a microcystic nail bed carcinoma? Am J Dermatopathol 2012; 34:549-552.

Subungual malignant tumors exhibiting the histologic features of tricholemmal keratinization are very rare and were described as onycholemmal carcinoma and malignant proliferating onycholemmal cyst. The authors observed a 58-year-old man with a 3-year history of recalcitrant painless onycholysis of the left middle finger. He had developed isolated symmetrical clubbing of all fingers since puberty. The affected nail was yellowish, even more curved and onycholytic. The excisional matrix biopsy showed a large multinodular tumor in the epidermis, without connection to the overlying epithelium. Histopathologically, numerous small tumor cell nests and larger nodules of basaloid to squamoid cells were present. Several small cystic areas with abrupt keratinization without a granular layer were seen, some of them showed calcification. There were ductal and cystic structures, the smaller of which appeared empty and the larger contained PAS and alcian blue positive material interpreted as mucin. Vacuoles forming a ring around the lumina and decapitation secretion were visible and interpreted as apocrine features. Occasionally, there were multivacuolated clear cells with scalloped

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nuclei reminiscent of sebaceous cells. The bulk of the lesion showed only low-grade malignancy, but there was a proliferation of large and anaplastic cells with hyperchromatic nuclei and many mitoses at the border of the lesion. The stroma was fairly sclerotic. The final treatment was distal amputation yielding the bulk of the carcinoma. The nail bed epithelium showed a focal granulosis and areas of high-grade epithelial dysplasia and focal invasion. A glandular differentiation was seen here. There were still areas of tricholemmal keratinization. Immunohistochemistry showed strong EMA positivity and very rare inner luminal areas were positive for keratin 19 and CEA. Keratin 7 and BEREP 4 were consistently negative.

Onycholemmal carcinoma is rare with only 3 cases reported in the literature. It differs from tricholemmal carcinoma by the absence of large lobular arrangement, clear cells and a thick basement membrane. The features of apocrine and sebaceous differentiation seen in this tumor have neither been described in onycholemmale nor in tricholemmal carcinoma before. Adenosquamous carcinoma is characterized by a merging of an ordinary squamous cell carcinoma with a component of adenocarcinoma, which has glandular areas and cystic spaces containing Alcian blue positive material and being keratin 7 and CEA positive. These latter features were not present in this case. Microcystic adnexal carcinoma is a distinct tumor of sweat gland origin, which may show some of the features present here. It demonstrates a triphasic appearance with keratinizing cysts in the superficial part, solid strands and nests in the middle and duct-like structures in the depth. Because of some similarities of the onycholemmal carcinoma with microcystic adnexal carcinoma, the authors propose to designate it as a microcystic nail bed carcinoma.

The normal nail may sometimes form multiple epidermoid inclusions in the nail bed. In Lewis' study of 87 autopsy cases, all 8 cases with clubbing had subungual epidermoid inclusions. These are microcysts probably originating from the nail bed epithelium. They do not form a granular layer. Epidermal keratinocyte stem cells can differentiate into keratinocytes and mucin producing cells. The authors speculate that a similar process might have led to the formation of this peculiar carcinoma. They also assume that the previously described onycholemmal carcinomas should be better classified as microcystic nail bed carcinomas originating from follicular microcysts of the nail bed without the peculiar environment of clubbing.

Chaser BE, Renszel KM, Crowson AN, Osmundson A, Shendrik IV, Yob EH, Drew GS, Callegari PR, Campbell S, Pitha JV, Magro CM. Onycholemmal carcinoma: A morphologic comparison of 6 reported cases. J Am Acad Dermatol 2013; 68:290-295.

Onycholemmal carcinoma is a rare malignant tumor originating from the nail bed epithelium. A few cases have been reported in the literature describing this slow-growing, subungual infiltrating neoplasm. Clinically, these cases have been described as warty, discolored, crusted, or ulcerative lesions that progress slowly until the patient presents with pain, swelling or onycholysis, at times associated with boney involvement. Histopathologically, onycholemmal carcinoma demonstrates solid collections of atypical keratinocytes and small keratin-filled cysts lined by atypical squamous epithelium devoid of a granular layer **(Fig 2)**. This type of abrupt keratinization is reminiscent of the pattern of trichilemmal keratinization described in the proliferating pilar tumor.

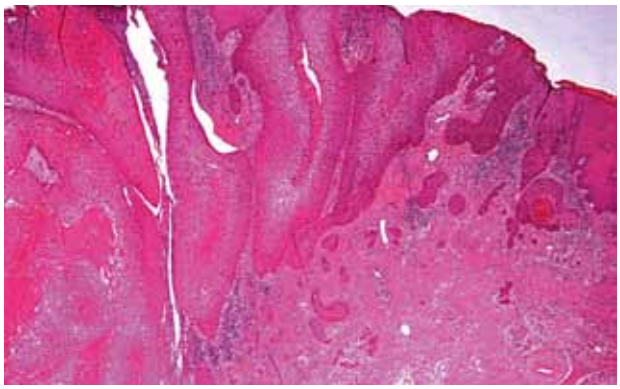

Fig2 - Onycholemmal carcinoma with large areas of clear cells reminiscent of follicle root sheath cells and small cystic formation with abrupt keratinization without a granular layer. © E. Haneke

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The authors report a series of 6 onycholemmal carcinomas and present the clinical and pathological features of this distinctive, but uncommon, variant of acral squamous cell carcinoma (SCC). There were 3 women and 3 men ranging in age from 39 to 84 years (mean age of 62 years). The known sites of involvement were the left fourth finger, right fourth finger, left great toe, left third finger, and right thumb. Among the clinical presentations were a non-healing progressive periungual ulcer of the nail fold, pain and swelling of the nail resembling paronychia, pain and swelling of the toe, painless keratotic plaque of the nail, and onycholysis, with erythema of the right thumb. In one case radiographic studies disclosed a soft-tissue defect and slight osteopenia, but no lytic and /or destructive lesion of the distal phalanx. The symptoms ranged in duration from 6 months to 5 years; in 3 patients the symptoms extended over a long unspecified period. Among the treatment modalities were Mohs micrographic surgery, radiation, excisional biopsy and debridement of the nail plate and distal nail bed, excision of the nail apparatus, and amputation. In the patient who underwent Mohs surgery, the final defect was closed by a V-Y advancement flap from the palmar side of the fingertip. At 1-month follow-up, the wound was well healed and the patient had recovered full function of her finger. There was no evidence of metastatic or recurrent disease in any of the patients, regardless of the treatment received. Histopathology appeared similar in all specimens.

There was an infiltrative squamoid lesion with variably sized lobules of squamous cells showing abrupt central keratinization without any interposed keratohyaline granules; an incomplete pattern of keratinization was not seen. The keratinization was most reminiscent of that seen in proliferating pilar tumors, but with enhanced atypia sufficient to categorize them as carcinoma. In one case, there was dystrophic calcification. In each case, foci of high-grade squamous atypia manifested by cells exhibiting high nuclear to cytoplasmic ratios and marked hyperchromasia were observed. Assessment of human papillomavirus (HPV) was negative in one case.

The authors assume that onycholemmal carcinoma originates in the nail isthmus located in the proximal nail bed immediately distal to the lunula. The sterile matrix/nail isthmus plays a critical role in the effective sealing of the nail bed by a very thin compartment of cornified cells, strongly adherent to the inferior border of the nail plate. This semi-rigid keratin produced through onycholemmal keratinization is also referred to as the solehorn. It increases the overall thickness of the nail, while maintaining its adherence to the nail bed. Onycholemmal carcinomas exhibit clinical features similar to other forms of carcinoma involving the nail bed and matrix including onycholysis, ulceration of the nail bed, or a verruciform distortion of the distal phalynx. The tumor is slow growing, reflective of its insidious and indolent nature, and in some cases the lesion may grow for years before a correct diagnosis is rendered. Bony involvement of the distal phalanx was described in 1 of 3 previously reported cases, with bone involvement also occurring in a similar case of malignant onycholemmal cyst. Regional lymph node metastasis and systemic spread had not hitherto been described.

Histopathologically, onycholemmal carcinoma is analogous to the proliferating pilar (or tricholemmal) tumors, although with sufficient atypia to warrant categorization as carcinoma. They have a lobulated and infiltrative growth pattern. The individual lobules demonstrate an abrupt pattern of keratinization devoid of a granular cell layer reminiscent of trichilemmal keratinization; small squamous pearls and cells exhibiting individual cell keratinization, which are morphologic findings in classic SCC, are noticeably lacking. The tumor can infiltrate the nail bed and extend into the dermis with potential to invade bone.

Perrin found that the distal nail bed (nail isthmus) and the outer root sheath of the hair follicle at the level of the isthmus both express CK5, CK6, CK16, CK17 and CK75. However, CD8/CK15, CK8, CK18, CK19 and CK7 were unique to hair follicle-derived keratins. Conversely the nail isthmus also shows expression of CK1 and CK10. Not surprisingly, in previously reported cases of onycholemmal carcinoma, follicular keratins were negative although CK6, CK14 and CK16 were positive. A link between HPV infection and digital and periungual squamous cell carcinoma has been noted in the literature, especially HPV-16, but this could not be confirmed for onycholemmal carcinoma in the one case examined.

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The differential diagnosis of onycholemmal carcinoma includes other tumors that affect the nail unit, such as squamous cell carcinoma, subungual keratoacanthoma, onycholemmal cysts/subungual epidermoid inclusions, and onychomatricomas. Onycholemmal carcinoma differs from (sub)ungual Bowen's disease and squamous cell carcinoma by its bland cytology and cystic spaces with tricholemmal (onycholemmal) keratinization. Also subungual keratoacanthoma has to be ruled out, as it may discern similar keratinization. In onycholemmal carcinoma, the cells exhibit overall cellular enlargement, high nuclear to cytoplasmic ratio, marked nuclear hyperchromasia, and nuclear contour irregularity. Onycholemmal horn shows a keratinization pattern similar to a tricholemmal horn and is well circumscribed without features of cellular atypia and invasion. Therapeutically, it has to be stressed that there was a favorable outcome in all cases, independent of their treatment, which spanned from radiation to amputation; it is therefore considered best not to amputate the digit, but to use Mohs surgery, conventional surgical excision or radiation therapy.

Okada K, Okada E. Novel treatment using thioglycolic acid for pincer nails. J Dermatol 2012; 39:996-999.

Pincer nails are characterized by an increasingly transverse overcurvature of the nail plate, principally affecting the big toenails, but often also the lesser toes, in a symmetrical fashion. Non-invasive treatment methods mainly rely on unbending the overcurved nail. However, this usually takes many months. A method has been developed for thick and short pincer nails that provides strong reduction by using thioglycolic acid (TGA). It acts by cleaving the disulfide bonds in the nail protein molecule, thereby softening the nail. Once TGA has been applied, the nail becomes soft and easy to bend or uncurve, whereas nails without TGA application remain stiff and difficult to bend. Other implements necessary for treatment include nail glue and nail repair powder for anchoring the wire and fixing the reduced nail, an elastic wire measuring 0.50-0.55 mm in outer diameter, a drill bit measuring 0.8 mm in outer diameter and a nail retractor.

Local anesthesia is unnecessary for simple deformity where a single wire is inserted from the distal edge. In severe deformity, where insertion of multiple wires on the proximal nail plate is required, a great toe digital block is performed. A hole is drilled into the nail at one or two sites with a 0.8-mm drill bit using an autoclaved drill. The hole is drilled manually. The drilling is stopped when the absence of drilling resistance is felt. A wire measuring 0.50 mm in diameter is inserted through the hole, bent backwards, and fixed using nail glue and nail repair powder on the opposite side in a patient with a thin nail plate. A 0.55-mm wire is required for a patient with a thick nail plate. After this procedure, mild reduction is achieved in some patients. To avoid skin irritation, the adjacent skin is masked with masking tape and a sponge, in which a large, round hole has been cut out, is attached to the nail. Thereafter, 5% TGA is applied thickly inside the cut-out sponge, directly onto the nail surface. The nail is then covered with plastic wrap to minimize contamination and leaking. The patient may need to wear open-toed sandals, or a shoe with the toe cut out, to ensure that the dressing remains in place. Six to seven hours after TGA application, the nail is washed with warm water and dried well. The wire is removed by a physician if adequate correction has been achieved. This nail is then immobilized using nail glue and nail repair powder in a reduced position. The aim of plastic fixation is to make adjustments to achieve an ideal reduction and to maintain the correction. Occasionally, the pincer nail is overcorrected by the action of TGA and the wire. However, the nail, which has been softened by TGA, can then be easily repositioned with an optimal curve once the wire has been removed. There is no need for a further visit to the outpatient clinic. Spontaneous removal is observed within 2 weeks.

The total time for this procedure is less than 30 min. The first stage, during which the wire is inserted and TGA is applied, takes 20 min. The second stage, which consists of washing and immobilizing the plastic phases, requires a further 5-10 min. After 10 procedures surgeons become proficient and fairly sophisticated at performing the technique.

A study was carried out on 104 patients and a good reduction of the 106 pincer nails was achieved within 1 to several days of the procedure. Reduction was achieved

within 1 day in 70 cases (66.0%), within 2-4 days in 32 cases (30.2%) and 5 days or more in four cases (3.8%). Untoward effects included one nail plate fracture, which was managed by applying a thin wire closely over the nail plate. Defluxion of the wire was seen in three cases and managed by drilling an additional hole or two to spread the reduction force. Bump formation on the median nail plate was observed in five patients, who were all aged over 70 years, and who did not complain of pain. The formations grew out within a few months. No recurrence was seen in a distal location once the nail deformity had been reduced. In eight cases (7.5%) moderate nail deformities that grew from the proximal portion were observed in the elderly patients within the 1-year follow-up period. They were re-treated with the same method.

All the patients were very satisfied with the treatment and none required invasive surgery. No post-procedure infection, skin irritation, continuous pain or nail cut out was evident. The results of the authors' treatment were thus considered favorable.

Surgical modalities have many disadvantages, such as prolonged wound healing, interference with daily activities and postoperative scarring. A recent randomized study revealed that partial matrix excision and orthonyxia were equally effective treatments for nail deformity, but the orthonyxia procedure showed better results with less postoperative morbidity and a shorter recovery time. A 79% rate of symptomatic improvement after insertion of cotton wool beneath the nail edge, and after follow up for a mean of 23.7 weeks, was seen. Effective pain relief was achieved with a resin splint treatment in 61 patients. However, the average duration of the resin splint application was 9.3 months and the recurrence rate was 8.3%. Arai et al. concluded that a plastic gutter splint, which needs only an average of 58.5 days, is the most effective treatment. Softening of the nail plate by applying TGA is a characteristic feature of the method described. TGA is a colorless liquid with a strong odor characteristic of mercaptans. TGA has been used as an active ingredient of permanent-waving solutions to avoid skin and hair irritation since the late 1950s. It is safe in concentrations of up to 15%.
The best treatment for nail deformity should be both effective and painless. There should be little postoperative discomfort, return to normal activities should be rapid, the percentage of complications should be low, the recurrence rate should be minimal and the outcome should be cosmetically acceptable. According to the authors, the method of softening the nail with thioglycolate and unbending the nail with elastic wire achieved satisfactory recovery without pain or postoperative discomfort in all the patients. The nail was greatly softened by the application of TGA and good reduction was achieved mechanically within a short period of time, mostly within 1-4 days. The rate of complications was negligible, and the recurrence rate was lower than that reported for other more conventional treatments. The outcome was cosmetically acceptable, because this method does not cause any scarring or nail narrowing. It is also useful for the treatment of nails that are too short and are difficult to treat with other conventional conservative methods.

Haricharan RN, Masquijo J, Bettoli M. Nail-fold excision for the treatment of ingrown toenail in children. J Pediat 2013; 162:398-402.

Ingrown toenails are a common ailment affecting both children as well as young adults. According to the view of the treating physician, surgical techniques for this condition can target the nail, the fold, or both. The most widely used method of treatment is wedge excision of the nail with matricectomy (surgical or chemical), focusing on the nail. Recurrence rates in excess of 10 to even 50% with poor cosmetic results, due to nail deformities, are common. As there is no difference between the diseased and control nails, the authors concluded that there was no justification to attack a non-existing deformity of the nail. In this publication, the nail-fold excision procedure described by Vandenbos and Bowers in 1959 in the US Armed Forces Medical Journal was used to treat children with ingrown nails. The procedure consists of an excision of the lateral and/or medial nail fold leaving a soft tissue defect to heal by secondary intention. Unlike other techniques, the Vandenbos procedure does not excise any part of the nail or the matrix.
The indications for the operation included failure to achieve relief of symptoms after an attempt of

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conservative management, which included non-steroidal oral analgesics and anti-inflammatory medications, shoe gear modifications, saline soaks, and rest.

The incision is started at the nail base, cutting out toward the side, and then up to the tip of the toe. The incision must be generous and adequate, including all the nail-fold skin. When removing the nail-fold skin, special care is taken not to damage the nail matrix at the proximal area of the incision. After removal of the nail-fold, the open skin edge and the subcutaneous tissue along the wound is cauterized with a Hyfrecator to minimize bleeding. The nail bed matrix is not cauterized. An antibiotic ointment followed by a nonadhesive gauze bandage is applied onto the open wound to facilitate the first dressing change. Then, several 5x5cm gauzes are applied, and finally the toe is wrapped snugly with a roll of 2" Sof-Kling gauze. Halfway through wrapping, the tourniquet is removed. The patient is kept for 15 minutes with the elevated foot resting on a pillow for hemostasis. 67 procedures performed on 50 (30 males, 20 females) patients were included in the study. Their mean age was 14 years (range, 9-18 years). The great toe was most commonly involved, and usually unilaterally. In 13 patients, there was bilateral great toe involvement and only 1 patient had a non-great toe (2nd toe) involvement. Most common nail-fold involvement was in the outer (lateral) fold in 48 of 50 patients, with isolated lateral fold involvement in 27 patients. In 23 patients, medial fold involvement was seen, with isolated medial fold involvement in only 2 patients. The patients were followed for a median of 14 months with a range of 6-28 months. No recurrences were noted in these patients during follow-up. All patients responded to the satisfaction questionnaire at follow-up or over the telephone. The average satisfaction score of these patients was 9.9 (SD 0.3), range 8-10.

The patients started normal ambulation in 7 days and resumed normal activities in 3-4 weeks; complete epithelialization occurs in 2 months. Typically, the healing process continues with excellent cosmetic results and virtually no scar.

Six patients had postoperative complications. Three patients had bleeding in the immediate postoperative period, which required a visit to the clinic and a change of dressing. None of these patients required repeated electrocoagulation or further intervention. One patient had nail deformity. The authors believe that it was related to excessive electrocoagulation in the proximal nail-fold close to the nail matrix, early in their series. Two patients (one with diabetes mellitus) had excessive granulation at 3 weeks postoperatively. Both were treated with silver nitrate (sticks) application with excellent results. The healing time, defined as complete epithelialization, takes 6-8 weeks. Given the absence of recurrence, the time required for complete healing is acceptable, and as shown in the survey results, it does not interfere with patient satisfaction. In adults, Vandenbos et al reported on 55 patients with no recurrences. Chapeskie et al evaluated this procedure on a mixed adult-pediatric population with excellent cosmetic results, no recurrences with a follow-up period of at least 12 months, and high rates of patient satisfaction. The main limitation of this study is that this is a case series and lacks an internal control cohort. However, the data was prospectively collected and is free from the bias associated with retrospective chart reviews.

Cordoba Diaz D, Losa Iglesia ME, Cordoba Diaz M, Becerro de Bengoa Vallejo R. Enhanced removal of phenol with saline over alcohol: an in vivo study. Dermatol Surg 2012; 38:1296-1301.

Ingrown toenails, also called onychocryptosis or embedded nails, are a frequent condition, which may considerably interfere with daily activities. It is treated by surgeons, GPs, orthopedic and podiatric surgeons, and dermatologists. A variety of treatments have been proposed of which phenolisation for partial nail matrix ablation is very often used with excellent healing rates. Phenol can be used instead of scalpel surgery both for partial and total matrix ablation. Detected by the German chemist Friedlieb Runge in 1834, phenol is an aromatic cyclical structure with a hydrogen atom replaced by a hydroxyl group. It is soluble in non-polar organic solvents, which are therefore used to treat acute phenol burns. Many reports describe the use of an alcohol as a lavage or neutralization at the end of the phenolization process in ingrown nails. Previous studies have shown that

alcohol lavage does not neutralize phenol, but may dilute it. At 20° C, 8.4 g of phenol can be dissolved in 100 ml of water, at 16° C only 6.7 g. , but at a temperature of 67° C, any proportion of phenol can be dissolved in water. The authors have therefore hypothesized that intraoperative lavage with physiologic saline would also be good to dilute the phenol left over from the procedure.

This hypothesis was tested using an automated cell diffusion chamber. A 1cm^2 piece of cadaver skin from the dorsal aspect of the foot was used. Both 96% ethanol and physiologic saline were used to irrigate the skin, after it had been treated with a hydroalcoholic phenol solution for 3 min. The results showed first that there was no diffusion of phenol through the skin, indicating that the phenol remains on the skin surface. Alcohol irrigation of the phenol treated skin recovered 27 mg of the applied 47.5 mg (56%) whereas washing with saline recovered 38.2 mg (80%) of the phenol (p=.004).

Phenolization of the lateral matrix horns is used by applying a cotton-tipped applicator dipped into liquefied phenol, for 30 sec to 5 min. After this, wound irrigation is often recommended in order to "neutralize" or remove excess phenol. This study has shown that alcohol does not neutralize phenol, but simply dilutes it. Since alcohol is toxic to white blood cells it is not recommended for use on open wounds. In contrast, saline is not volatile or irritant, does not interfere with basic wound healing and defense mechanisms - and was shown to be more efficient in removing excess phenol. The authors conclude that due to the caustic nature of phenol and the extensive necrosis, persistent exudation and pain, as well as post-phenol periostitis, it is advisable to eliminate any residual phenol from the wound.

COMMENTARY E. HANEKE

Of all malignant tumors in dermatology, melanoma attracts most attention. There are still a lot of misconceptions, not to say mystifications of melanomas, both of skin and nails. It is however, a fact that early subungual melanoma can be extremely difficult to diagnose histopathologically, even for the experienced nail pathologist. This short letter by Weedon, a master of dermatopathology, is therefore welcome as it might aid the dermatopathologist to make a correct diagnosis in very early cases also or to correctly interpret the advancing edge of a melanoma.

Malignant keratinocytic tumors of the nail are mainly Bowen's disease and conventional squamous cell carcinoma. Onycholemmal carcinomas are quite rare with a total of about 10 cases published. They are true adnexal tumors as they originate from the nail bed. As we know from adnexal tumors of follicular origin, many additional features are possible. It is therefore not surprising that this has also been observed by Perrin and colleagues. The American series of 6 onycholemmal carcinomas is outstanding. Their main objective is that this carcinoma can be treated with conservative surgery and that amputation is not necessary.

The various forms of ingrowing nails still attract many clinicians and clinical researchers. Pincer nails belong to the group of conditions frequently seen in individuals over 30 years of age, although they are rarely observed in young adults. The treatment is tedious, time-consuming, and often not satisfying. Surgical options are limited despite the many techniques published and most of them include narrowing of the nail plate. This is effective in mild cases and works by taking the outward pressure off a very wide base of the distal phalanx from the matrix horns **(Fig 3 a,b)**.More demanding surgery includes nail bed plasty with flattening of the pinched nail bed. The Japanese authors have now proposed an ultrafast

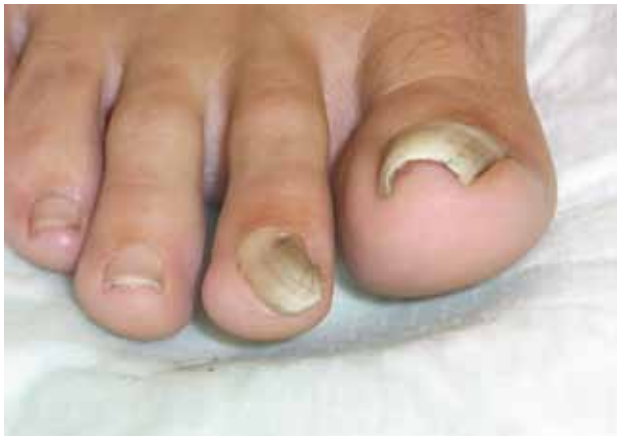

Fig3a - Pincer nail. © E. Haneke

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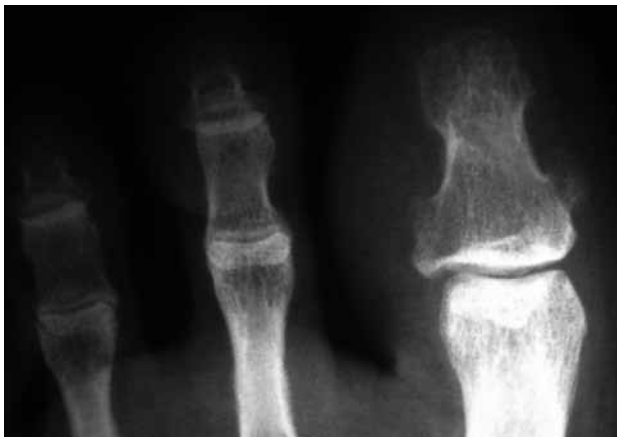

Fig3b - The radiograph shows a lateral basal exophyte of the terminal phalanx of the hallux. © E. Haneke

technique compared to conservative flattening of the nail by applying thioglycolate to the nail plate to soften it, i.e. to unbend it more easily. The results shown after one day of treatment of an overcurvature of almost 360°, together with a flat nail bed, appear virtually incredible. Unfortunately, the follow-up period is very short and the authors do not at all discuss the pathogenesis of overcurved nails. They also fail to give details as to the kind of wire they introduce.

A Spanish group that has already published on different aspects of phenol use for ingrown nails has now compared alcohol and physiologic saline for the dilution of phenol, which might be of relevance after matrix horn phenolization. They found that physiologic saline removes residual phenol better than alcohol, that phenol is not neutralized, and finally that phenol in their test chamber did not penetrate skin. This is why their conclusion that phenol should be removed in order to prevent phenol toxicity and irritation does not appear to be justified.

There are two opposing views on the pathogenesis of ingrown nails: either the nail is at fault or the periungual tissue. For those who call the disorder onychocryptosis, it is the lateral nail fold that may be hypertrophic. Different techniques exist to remove the hypertrophic lateral nail fold in order to free the lateral nail plate margin. They vary a bit in radicality and thus in postoperative morbidity. The authors present here the results of a pediatric cohort that underwent generous excision of the lateral nail folds. While they claim to have only good results, the morbidity of their patients lasted 4 to 6 weeks as compared to only some days after phenolization. The main argument for nail fold removal is that the nail plate is not narrowed. However, virtually all the cases shown in this publication have wide and very curved nails. The cosmesis after narrowing the nail by taking away the vertically positioned lateral margin is almost as good as that of a large nail with a 180° curvature.

Jose Maria MASCARO

Capillaroscopy in systemic diseases & psoriasis

Rossi D, Russo A, Manna E, Binello G, Baldovino S, Sciascia S, Roccatello D. The role of nail-videocapillaroscopy in early diagnosis of scleroderma. Autoimmun Rev. 2013; 12: 821-5.

Raynaud phenomenon (RP) is a common event with considerable prevalence in the general population.[1] It is a clinical sign of precocious abnormal microcirculation that can be considered as an early clinical manifestation of systemic diseases, more precisely, a typical manifestation of vascular involvement in systemic scleroderma (SS). Nailfold video-capillaroscopy (NFC) is at present the most valuable tool for an early diagnosis of SS and other connective tissue diseases (CTD). Detection of capillaroscopic patterns (the so-called "SS-pattern": giant capillaries, hemorrhages, avascular areas and necrosis; with three progressive steps named "early", "active" and "late") and follow-up of patients using this method, with intervals of a few months[2,3] is a useful non-expensive and non-invasive method of monitoring the progression of SS.

Ribeiro CF, Siqueira EB, Holler AP, Fabrício L, Skare TL. Periungual capillaroscopy in psoriasis. An Bras Dermatol. 2012 Jul-Aug;87(4):550-3. PubMed. PMID: 22892767.

Cutaneous microcirculation is different in psoriatic patients (PsP) and normal individuals. Vascular changes have been reported in nailfolds of PsP.[4] For this reason Ribeiro et al studied NFC in 46 psoriatic patients (mean age 50.5, median disease duration 10 years) and 50 healthy controls and they found lower capillary density, increase of avascular areas and morphologically abnormal capillaries in psoriatic subjects. No association of changes of capillary density and duration, extent and severity of the disease was noted. However the presence of avascular areas was more common in patients whose nails were affected by the disease (pitting or dystrophies).

Bhakuni DS, Vasdev V, Garg MK, Narayanan K, Jain R, Mullick G. Nailfold capillaroscopy by digital microscope in an Indian population with systemic sclerosis. Int J Rheum Dis. 2012; 15: 95-101.

Twenty two patients with "diffuse" cutaneous systemic sclerosis (DSS), 20 "limited" cutaneous systemic sclerosis (LSS) and 42 controls were evaluated by NFC with the aim to establish the utility of an inexpensive digital microscope. The authors found a significantly lower capillary density in all systemic sclerosis cases compared to controls. Disorganized capillary architecture was significantly more common in DSS than in LSS. The "scleroderma pattern" (SP= avascular areas, definitely enlarged or bushy capillaries and complete distortion of the normal regular capillary pattern) was present in 81.9% of DSS and 75% of LSS. Only 4% controls had a "non specific pattern" (tortuous, crossed or mildly enlarged capillaries) and none of them showed SP.
The authors specifically conclude that NFC findings in systemic sclerosis are related to the disease subset. However, it is also important to emphasize that a cheap and widely available equipment - a digital microscope with an inbuilt camera - gives similar results to those obtained in previous studies using more sophisticated and expensive instruments.

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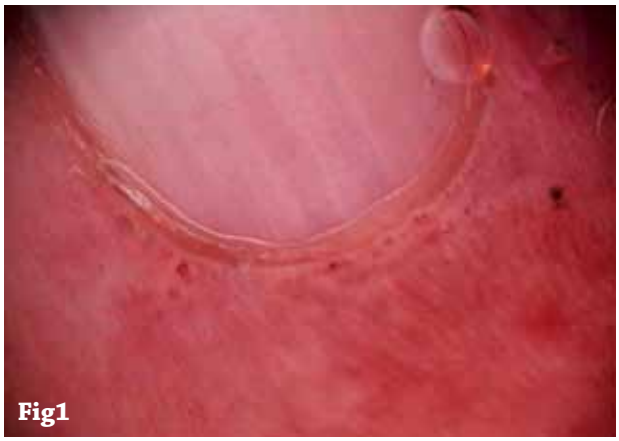
The relevance of vascular alterations in connective tissue diseases, and particularly in scleroderma, is well known **(Figs 1 & 2)**. However, the nature of endothelial injury is still not easily evaluated and definite markers of endothelial injury continue to be studied. For this reason, the assessment of microvascular function by laboratory methods is not specific or sensitive (Rossi et al.). On the other hand NFC is a non invasive technique that could be used in practically all individuals permitting the study of superficial blood capillaries. This technique has been very useful for diagnosis and prognosis of diverse systemic diseases, particularly auto-immune connective tissue diseases.

The nail in systemic diseases

Jose Maria MASCARO



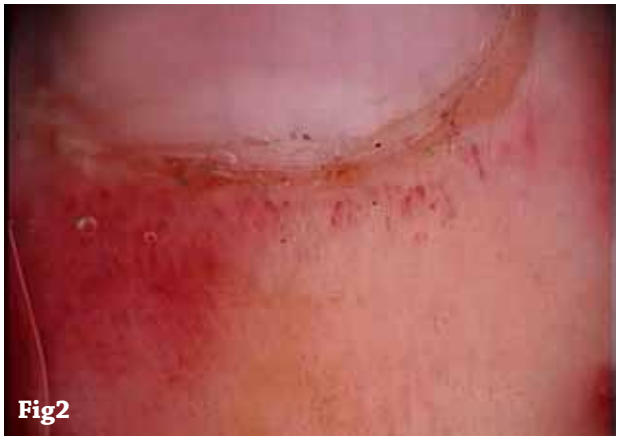


Fig1 & 2 - Capillaroscopy images (x30) in two patients with systemic sclerosis (digital epiluminescence dermoscopy). Enlarged capillaries, haemorrhages and areas of capillary loss are visible. (Collection of the Departement of Dermatology and Rhumatology. Hospital del Mar. Barcelona. Spain)

Fig3 - Typical giant capillary of the nailfold. © D. Rossi et al (Autoimmun Rev 2013)

Raynaud phenomenon (RP) is the first manifestation in approximately 90% of cases of SS. However, there is also a prevalence ranging from 2% to 22% of the general population [3,5] and there is a general consensus that all individuals who present RP should undergo a capillaroscopic examination to evaluate if there is a risk of developing a systemic disease. 12% of subjects with a presumed primary SP developed an underlying causal disease (Bhakuni et al.). Of course this method has only about a 50% positive predictive value, but this percentage is still higher than that obtained by any other method. Moreover NFC is a non-invasive, easy and inexpensive procedure. Many papers have now been published in journals specialized in internal medicine, dermatology, rheumatology, angiology and ophthalmology demonstrating the utility of this technique.[6-8]

NFC has been proved valuable, not only in autoimmune connective tissue diseases and some dermatological disorders, but in the study of many other extra-rheumatic or dermatological conditions, such as arterial hypertension, diabetes mellitus, acromegaly, hyperthyroidism, cardiac syndrome X, primary biliary cirrhosis, Crohn's disease and familial Mediterranean fever.[9] Patients with tortuosity of retinal arteries (a familial disease producing vision alterations due to hemorrhages caused by minimal traumas) may associate visible tortuosity of nailfold capillaries.[8] This capillary syndrome appears to be systemic and therefore, NFC could additionally be of help in the study and control of these patients.

Vascular microcirculation of the skin in psoriatic patients is peculiar and appears to be different to that seen in subjects without the disease. Blood flow seems to increase in the lesions[10,12] and vascular changes precede their onset. These changes have even been observed in non affected skin[12,13] and are associated with raised local levels of angiogenic factors, such as transforming growth factor beta (TGFbeta), platelet growth factor (PDGF) and vascular endothelial growth factor (VEGF)[14,15] that return to normal when the clinical lesions clear. In a limited report (only 18 cases) Salli et al.[16] observed a relation of morphological micro-vascular changes and decreased capillary density in mutilating psoriatic arthritis **(Fig 3)**.

The conclusion of Ribeiro et al that psoriatic patients have decreased capillary density and increased morphologically abnormal capillaries in nailfold skin is relevant and maybe this finding could be useful to predict the evolution and development of articular complications.

Finally, we would like to emphasize that Bhakuni et al underline that, in spite of its usefulness, video-capillaroscopy is still an under-utilized method due to the cost of the current equipment systems (these authors estimate the price to be between 46.000 and 98.700 US $). They consider that the consequence of this is a lack of expertise in many hospitals and countries unable to afford it. For their study they used an easily available and inexpensive instrument (55 to 135 US $ according to Bhakuni et al): a digital microscope with inbuilt camera that was attached to a computer via a USB port; this low-cost, pocket sized, easily available equipment appears to be able to generate good quality images (20x - 200x) which can easily be stored in a computer. Other studies made with inexpensive equipment, such as an ophtalmoscope, a dermatoscope or a light microscope gave low resolution, low magnification and non reproducible results.
These comments upset us, because, if most authors are convinced that NFC represents the most reliable tool for studying microvascular changes in CTD, it is extremely important that researchers, potential users and the medical industry concentrate and focus on the development of more simple, but efficient, optical systems to enlarge NFC availability and utilization. This technique must be obtainable for all doctors who need it. Nearly all dermatologists have or can easily obtain a dermatoscope as well as other similarly effective, inexpensive and useful tools. I hope that in the near future it will be analogous with more simple but efficient NFC devices for dermatologists as well as for rheumatologists and internal medicine specialists.

To summarize we can affirm that nailfold capillaroscopy, that has been tested for quite a long time, must be integrated into the list of non-invasive explorations to teach dermatologists and should be used, not only for the purpose of diagnosis, but also to help in providing data to evaluate progression and severity of an increasingly long list of skin and internal diseases.

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Bianca Maria PIRACCINI

Onychomycosis

Rios-Yuil JM, Bonifaz A, Arenas R, Araiza J, Fernández R, Mercadillo-Pérez P, Ponce-Olivera R. Mycological studies of nail samples obtained by curettage vs. vertical perforation of the nail plate. J Eur Acad Dermatol Venereol. 2012 Nov 20. doi: 10.1111/jdv.12035. [Epub ahead of print] PubMed PMID: 23167509.

The study compared the percentage of positivity of direct microscopy and culture of nail specimens obtained with 2 different sampling techniques: curettage (scraping) **(Fig 1)** and vertical perforation (drilling) **(Fig 2)** of the nail. Curettage resulted significantly better than drilling in giving positive results of both direct microscopy and cultures. The authors conclude that drilling is not a recommended method for sampling nails with onychomycosis, because it is also more complicated and time consuming than curettage.
It is interesting to note that overall, up to 36% of the direct microscopy examinations and 78% of cultures resulted negative.

Fig2 - Nail sampling for mycology by drilling: the nail plate is vertically perforated in order to reach the subungual scales. © B-M. Piraccini

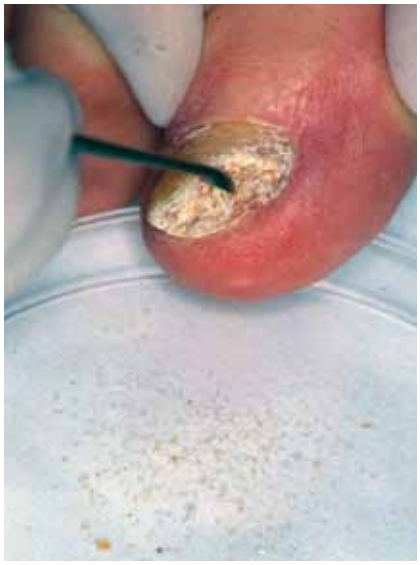

Fig1 - Nail sampling for mycology by curettage: the onycholytic nail plate has been clipped away and the scales are scraped with a curette. © B-M. Piraccini

Shemer A, Davidovici B, Grunwald MH, Lyakhovitsky A, Amichai B. Onychomycosis: a simpler in-office technique for sampling specimens. J Fam Pract. 2012; 61:552-4. PubMed PMID: 23000663.

The study assessed the accuracy of distal nail sampling, without removal of the onycholytic nail plate, for mycological examination of onychomycosis. Mycology from the distal nail was performed in 160 cases of previously confirmed onychomycosis. Distal sampling was performed by first scraping the distal nail bed, and secondly the underneath of the nail plate without removing the detached nail plate, but only paring its most distal part. The distal nail bed gave a higher percentage of positive KOH and cultures than the underneath of the nail plate. The combined results permitted a higher percentage of diagnosis. The authors concluded that sampling first the underneath of the distal nail and then the distal nail bed is an accurate way to perform mycology in onychomycosis.

Onychomycosis

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Hui X, Lindahl A, Lamel S, Maibach HI. Onychopharmacokinetics of terbinafine hydrochloride penetration from a novel topical formulation into the human nail in vitro. Drug Dev Ind Pharm. 2012 Aug 9. [Epub ahead of print] PubMed PMID: 22873754.

This in vitro study evaluated nail penetration by terbinafine in a new vehicle that should enhance drug penetration into the nail plate. The new formulation contains substances that soften and hydrate the nail plate, such as ethylacetate, propylene glycol, urea, polymethylmetacrylate, lactic acid, Tween 80, sodium hydroxide, and EDTA. The nail models were human healthy fingernails taken from cadavers and kept matching in vivo conditions of temperature and humidity. The topical formulation, containing radiolabeled terbinafine, was applied on the nail plate once a day for 14 days. Terbinafine concentrations in the different parts of the nail plate (dorsal, ventral and intermediate) and its undersurface were then measured by looking at the amounts of radioactivity. After 14 days, the concentrations of terbinafine in the deep nail plate and its undersurface were higher than those reported after systemic administration of the drug and always well above the MIC for most dermatophytes.

Sigurgeirsson B, Ghannoum M. Therapeutic potential of TDT 067 (terbinafine in Transfersome): a carrier-based dosage form of terbinafine for onychomycosis. Expert Opin Investig Drugs. 2012 Oct;21(10):1549-62. Epub 2012 Aug 9. PubMed PMID: 22876754.

The study reviews data about the effectiveness of a new carrier-based dosage form of terbinafine in the treatment of onychomycosis. The innovation of the product relies on a lipid-based drug carrier, which is composed of complex lipid vesicles that are able to cross the epidermis and reach the dermis, driven by the transcutaneous water gradient. The mechanism by which the carrier delivers the drug to the nail bed is not known, but possibly relies on drug delivery in the skin surrounding the nail. The article reviews in vitro and in vivo studies on the effectiveness of terbinafine 1.5% in the new vehicle. In vitro studies showed that terbinafine carried by this delivery has a higher fungicidal activity against dermatophytes than conventional preparations of terbinafine and it is also effective on non-dermatophyte molds and yeasts. In vivo phase II studies evaluated the effectiveness of terbinafine in tranfersomes in a spray that the patients applied on the nail and periungual tissues twice a day for 12 weeks. At week 14, two weeks after the end of treatment, 91% of the treated nails were mycologically cured (KOH and culture). 12 weeks after interruption of therapy the cure rate decreased to 80%. The high cure rate is possibly explained by the fact that the vehicle allows terbinafine to enter the fungal cell, potentiating its antifungal effects. Evaluation of the clinical effectiveness revealed that 40% of the treated nail showed signs of growth of new clear nail during treatment, but not after its interruption. This low percentage was explained by the shortness of the period of treatment. Local side effects (redness, irritation, burning) were reported by 30% of the patients, sometimes only after the first application of the product and also at other times during all the study period. Blood testing revealed absence of systemic absorption of the drug. Phase III studies of the product are currently ongoing.

Sipponen P, Sipponen A, Lohi J, Soini M, Tapanainen R, Jokinen JJ. Natural coniferous resin lacquer in treatment of toenail onychomycosis: an observational study. Mycoses. 2012 Nov 6. doi: 10.1111/myc.12019. [Epub ahead of print] PubMed PMID: 23131104.

The study tested the efficacy of a lacquer, containing the resin of the natural coniferous Norway spruce (Picea abies), in the treatment of onychomycosis. The lacquer, with 30% of the resin, was applied daily for 9 months on nails with ”a clinically probable diagnosis of onychomycosis”. This clinical diagnosis was performed by 3 physicians: an orthopedic surgeon, a cardiothoracic surgeon and a pathologist. The absence of a trained dermatologist may explain why the pictures presented, of extremely poor quality, show nails altered in different ways and more suggestive of onychogryphosis, traumatic onycholysis and psoriasis than for onychomycosis! Mycology (KOH and cultures) was performed before the start of the treatment

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and after 9 months (after a 4-week washout period). The results are not easy to understand and evaluate, as they vary in the different tables and in the result section and are not divided according to the type of nail invasion! It seems that 9 out of 14 (or 13 out of 19!) patients with positive mycology turned negative at the end of the study period. Complete clinical cure was obtained in 3 cases, all with negative mycology at the study entry! The authors explained the effectiveness of the resin lacquer in onychodystrophies that were mycologically negative by the fact that the resin may be effective in diseases other then onychomycosis,such as nail eczema and nail psoriasis. But the study was about onychomycosis! Finally, the names of the 3 physicians who performed the study can be seen in the conflicts of interest section, and they are all shareholders in the company that markets resin-based medical products...

Emtestam L, Kaaman T, Rensfeldt K. Treatment of distal subungual onychomycosis with a topical preparation of urea, propylene glycol and lactic acid: results of a 24-week, double-blind, placebo-controlled study. Mycoses. 2012Nov;55(6):532-40. doi: 10.1111/j.1439-0507.2012.02215.x. Epub 2012 Jun 11. PubMed PMID: 22681227.

The authors evaluated the effectiveness of a new topical preparation containing urea, lactic acid and propylene glycol on onychomycosis in a randomized-placebo-controlled study involving more than 500 patients. The tested product was thought to be efficient in fungal infection because of the keratolytic, antimicrobial and hydrating actions of the 3 components and from the osmotic effect of propylene glycol. Enrolled patients, suffering from distal subungual onychomycosis due to dermatophytes involving <75% of fingernails and/or toenails, applied either the tested product or the placebo on the nail and underneath its free edge at bedtime for 24 weeks. A surgical tape was wrapped around the treated nail for the first 4 weeks of treatment. The results showed that the tested product induced a higher mycological cure than the placebo: the rate of patients with negative mycology at 24 weeks was 27% (product) vs 10% (placebo). The authors suggested that longer treatment periods may promote higher success rates. The patients' comments about the evolution of their onychomycosis showed that those who had used the tested product experienced more improvements and cures than the patients using the placebo. Both topicals were considered very easy to apply by the vast majority of patients. About 14% of the patients using the tested product experienced a discoloration of the treated nail that became white and opaque on the side affected by onychomycosis, and about 8% experienced onycholysis. The most frequent side effect of the tested topical product was, however, damage to the soft tissues around the application side: more than 20% of the patients reported skin irritation, erythema and pain in the periungual area. Interruption of treatment due to these side effects was reported in 1.7% of the treated patients. The authors suggested that the side effects on the skin of the tested products could be due to the application of an excessive amount of the product.

COMMENTARY B.M. PIRACCINI

Onychomycosis is a very common problem in the adult population, with a prevalence reaching up to 34% in people aged 65 and over.[1] Considering the clinical features, it is easy to understand why studies on the impact of onychomycosis on patients' quality of life give impressive data.[2] Patients with onychomycosis have an impaired quality of life, especially when the disease is severe, due to the cosmetic changes of the affected nails **(Fig 3)** and sometimes due to impaired function: when the toenails are thickened, wearing shoes may be difficult **(Fig 4)**. People with fingernail onychomycosis **(Fig 5)** have difficulty in carrying out manual activities and are also severely distressed by the cosmetic aspect. It is therefore not surprising that the search for an optimal treatment for this disease is still ongoing, with new studies being carried out all over the world. Most of the studies, such as the ones reviewed here, are about topical therapies, as they are easier to prescribe and better accepted in the older population.

However, not all nail dystrophies are due to onychomycosis and more than 50% of the patients who consult for nail abnormalities are actually affected by other nail diseases, mainly from traumatic and inflammatory origin (BM Piraccini, personal experience). Differential diagnosis often requires mycology, which should be carried out in

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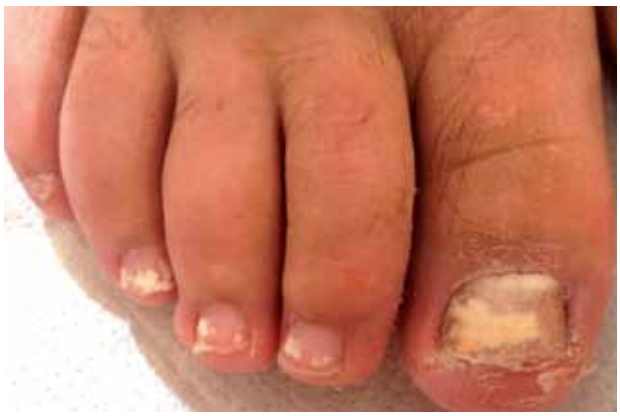

Fig3 - White superficial onychomycosis due to Trichophyton interdigitale of several toenails. The patient came to consultation due to the impaired nail cosmetic function. © B-M. Piraccini

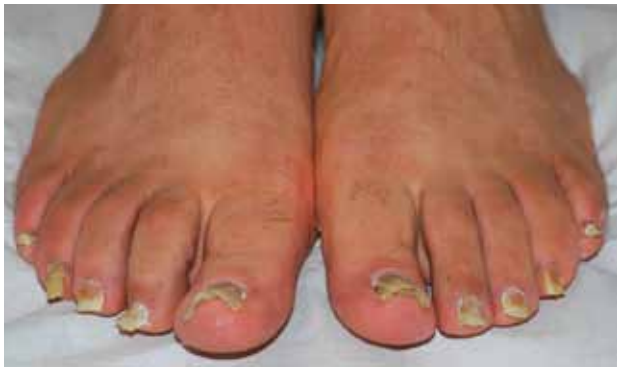

Fig4 - Distal subungual onychomycosis due to Trichophyton rubrum of several toenails. The nails are thickened and yellow white in color. Wearing shoes may be painful. © B-M. Piraccini

Fig5 - Fingernail onychomycosis due to Trichophyton rubrum. The nails are detached and friable, with diffuse white discoloration. © B-M. Piraccini

a reliable way. A very important step in the mycological study of onychomycosis relies on nail sampling. An adequate sampling must contain enough material and live fungal species. The material should in fact be utilized both for microscopic examination, which is able to detect fungal hyphae, dead or alive, and for culture, which permits to isolate the fungus that causes the nail infection. In particular, in disto-lateral subungual onychomycosis, which is the most common type, sampling for mycology should be carried out in the most proximal area of nail invasion. This is due to the fact that, in this clinical variety of onychomycosis, fungi reach the nail from the plantar skin and invade the distal part of the subungual space and then progress proximally.[3] Vital hyphae are therefore most likely to be found in the site of progression of the onychomycosis, which is the most proximal area.

Sampling for mycology is usually carried out by clipping away the detached nail plate, followed by gentle scraping of the subungual scales close to the healthy nail. The article by Rios-Yuil et al, which compared the mycology outcome of specimens obtained by clipping and curettage versus that obtained with the use of a medical drill to perforate vertically the nail plate, recommends clipping and curettage as the simplest and most trustable method. It is also the cheapest, as all dermatologists possess nail clippers and curettes! However, sometimes patients do not like to have a large part of the nail plate removed, because they are afraid it will be painful or they simply want to cover the diseased nail with a colored polish to hide it. For this reason, the second article by Shemer and colleagues, suggests that it is possible to avoid nail clipping by performing distal nail sampling. The technique is reliable, even if more time consuming than simple clipping and curettage. Moreover, removal of the infected part of the nail should always be recommended, since it favors good outcome after therapy.

The other reviewed articles are all about new topical antifungals in onychomycosis. More and more articles about new topical agents and new topical modalities of drug delivery for fungal nail infection are being published, and when one reads the results, they all seem to be effective! A good way to understand if a product may be promising for the treatment of onychomycosis is to first read its background and the material and methods section, in order to have an immediate idea of how the

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study was carried out. Topical products for onychomycosis containing antifungal drugs should be initially tested in vitro, dosing the drug concentrations in the different parts of the nail plate after application. The concentration reached in the deep nail plate and its undersurface should be above the MIC for dermatophytes in order to indicate possible in vivo effectiveness.

In vitro drug tests are then followed by in vivo studies, which permit the evaluation of the antifungal effect in terms of clinical and mycological efficacy, the monitoring of product safety and the assessment of patients' appreciation of the product. Clinical and mycological cures are both mandatory to have a valuable topical product, as is the product tolerability. Negative mycology is usually reached earlier than clinical cure, since the latter requires complete growth of a healthy nail replacing the diseased one. This may take months. In my opinion, duration of studies with topical antifungal agents is usually too short - around 24 weeks - to permit a good percentage of mycological and clinical cure. In clinical practice, we do not obtain cure of distal subungual onychomycosis in less than 5-6 months, and the duration of therapy is even longer when fungal invasion involves more than two thirds of the nail.

Product tolerability and patients' satisfaction are other important topics. A topical product should be easy to apply with a dispenser that allows application of the correct amount. Since it is difficult to avoid spreading the topical on the periungual tissues, the product should carry a very low risk of skin irritation and maceration. This may be difficult to achieve specially in long-term use with keratolytic agents, including urea and lactic acid, which frequently induce irritant contact dermatitis that may be bothersome for the patient **(Fig 6)**.

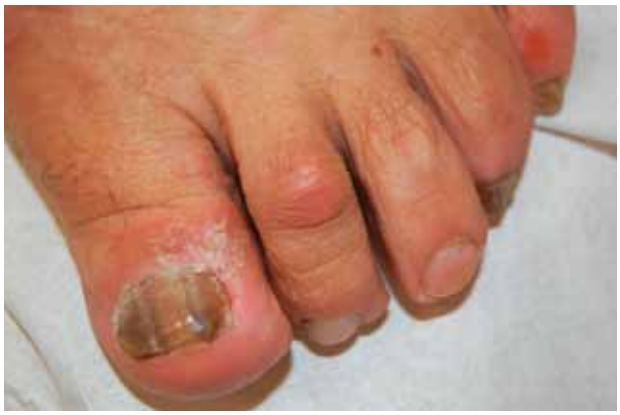

Fig6 - Periungual erythema and scaling in a patient with distal subungual onychomycosis, who was applying a topical agent with keratolytic effect on the nail plate. © B-M. Piraccini

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Bertrand RICHERT

2012 Highlights

Markova A, Weinstock MA. Risk of Skin Cancer Associated with the Use of UV Nail Lamp. J Invest Dermatol. 2013; 133: 1097-9.

Research has highlighted the carcinogenic dangers of tanning bed exposure. UV nail lamps are increasingly used for professional and personal nail techniques **(Fig 1)**. The authors sought to better quantify the effect of UV radiations emitted by UV nail lamps in nail salons and compare their carcinogenic potential with exposure of narrowband UVB (NBUVB) used for phototherapy. NBUVB is viewed as low risk, although not as zero risk, in the development of carcinoma. Three devices were selected among the hundreds of UV nail lamps because of their widespread availability in nail supply stores. UV nail lamps contain either fluorescent bulbs or light emitting diode lights. UV nail lamps primarily emit UVA with no detectable UVB or UVC. Spectral irradiance in the plane of the nails was measured from several locations within each device. The authors then calculated the carcinogenic equivalence in terms of NBUVB courses. Over 13,000 fluorescent bulbs devices and more than 40,000 light emitting diode light sessions each lasting for 10 minutes would be required to equal the UV dose received during one NBUVB session. This means that one would need over 250 years of weekly UV nail sessions to experience the same risk exposure as a single treatment of NBUVB (15 to 30 sessions of NBUVB over 5 to 10 weeks). The authors conclude that UV nail lamps do not appear to significantly increase the lifetime risk of carcinomas and that dermatologists and primary-care physicians can reassure patients regarding the safety of these devices.

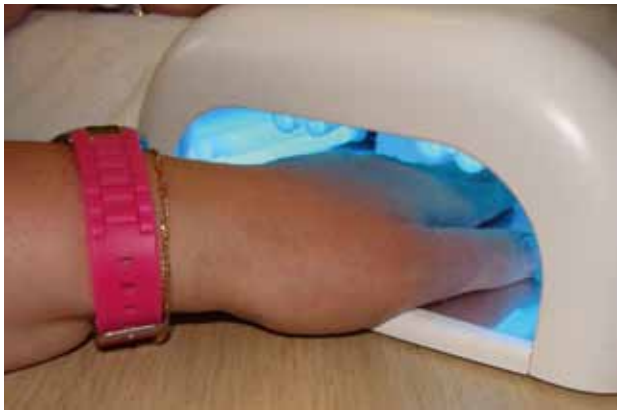

Fig1 - UV lamp for acrylic nails. © B. Richert

Diffey BL. The risk of squamous cell carcinoma in women from exposure to UVA lamps used in cosmetic nail treatment. Br J Dermatol. 2012; 167:1175-8.

Ultraviolet (UVA) lamps have been used in the nail cosmetic industry for more than three decades. A report that two women, who had undergone this treatment, subsequently developed squamous cell carcinoma (SCC) on the dorsum of their hands has prompted some concern about the safety of this procedure. The purpose of this paper was to objectively estimate the risk so that users of UVA nail lamps could be advised appropriately. A mathematical model that combines age and UV exposure was used to compare the risk of developing SCC due to typical sun exposure, with the risk of inducing these cancers from exposure to UVA nail lamps. The analysis indicates that it would be necessary for tens or hundreds of thousands of women to use a UVA nail lamp regularly for one to develop SCC on the dorsum of the hands as a direct consequence. The authors conclude that this is a very low risk and one that is likely to be accepted by most women. Also wearing fingerless gloves, when the hands are being exposed to UV radiation, can reduce the risk to virtually zero.

Dika E, Patrizi A, Fanti PA, Alessandrini A, Sorci R, Piraccini BM, Vaccari S, Misciali C, Maibach HI. Two synchronous periungual BCC treated with Mohs' surgery. Nail polish related? Cutan Ocul Toxicol. 2013; 32:161-3.

The nail unit is an unusual location for basal cell carcinoma (BCC) and only 25 cases have been reported in literature up to now. It is well known that chronic exposure to chemical agents may initiate a BCC. Nail polishes contain numerous chemicals, but the common potentially toxic ingredients are formaldehyde, toluene and dibutyl phthalate. US and ECC health organizations are putting pressure on

Bertrand RICHERT

nail polish manufacturers to reduce or eliminate toxic ingredients from their products. The authors report here the case of a 73 year-old lady, without any relevant medical history, who developed two synchronous BCC on the proximal nail folds of two fingers over several months. The lesions appeared after she had regularly used a "made in China" nail polish for three years. The ingredients were not specified on the bottle. The authors discuss the potential role of nail lacquer in the development of the two BCC.

Hollmann TJ, Bovée JV, Fletcher CD. Digital fibromyxoma (superficial acral fibromyxoma): a detailed characterization of 124 cases. Am J Surg Pathol. 2012; 36:789-98.

This report details the histologic and clinical findings in a large series of 124 cases of superficial acral fibromyxoma. There were 70 male and 54 female patients (1.3:1, M:F), with a mean age of 48 years. The average tumor size was 1.7 cm. Half of the patients presented with a painful mass on the hands (52%) or feet (45%), with rare tumors arising on the ankle or leg. Most tumors occurred on the digits with the majority growing in close proximity to the nail (97% on fingers, 96% on toes) **(Fig 2)**. Histologically, 80% of the cases were poorly marginated; 70% infiltrated the dermal collagen, 27% infiltrated fat, and 3% invaded bone. In the cases where imaging studies were available, bone involvement due to an erosive or lytic lesion was more frequent (9/25, 36%). All tumors were composed of spindle-shaped or stellate-shaped cells with a loosely fascicular growth pattern separated by dense hyaline collagen alternating with myxoid stroma. Increased mast cells were noted in 88% of the tumors. All tumors included cells with minimal atypia. Tumor cells were reactive for CD34 in 69%. All tumors were negative for S100. Follow-up was available in 47 cases and ranged from 1 to 252 months. 24 % of the tumors recurred locally within 2 years. All of them were in the vicinity of the nail unit, either on the fingers or the toes. All recurrent tumors had positive margins on excision and no other clinical or pathologic features correlated with recurrence/persistence. To date, no tumor has metastasized.

Lurati M, Baudraz-Rosselet F, Vernez M, Spring P, Bontems O, Fratti M, Monod M. Efficacious treatment of non-dermatophyte mould onychomycosis with topical amphotericin B. Dermatology. 2011; 223:289-92.

The aim of this work was to report the efficacy of a topical amphotericin B solution on non-dermatophytes molds (NDM) onychomycosis in a series of 8 patients resistant to multiple conventional treatments. The infectious agent, identified by cultures and PCR/RFLP, was *Fusarium* sp., *Acremonium* sp. and *Aspergillus* sp. in 6, 1 and 1 cases, respectively. Intravenous solution of amphotericin B was reconstituted in a 50:50 mixture of dimethylsulphoxide and 2-propanol at a final concentration of 2 mg/ml. The resulting solution was stored in amber glass bottles with a dropper and protected from light with aluminium foil. Patients applied 1-3 drops of the solution once a day to each affected nail and briefly let the solution evaporate. No other mechanical debridement or medications were allowed except for trimming the nails as short as possible. All patients were clinically cured after topical amphotericin B therapy at a 12 months follow-up. Mycological cure was observed in 7 out of the 8 patients. Residual filaments could still be observed on microscopic examination in one of the patients, even though the nail appeared clinically normal. There were no drop-outs, no local or systemic side effects. The authors conclude that topical amphotericin B is an efficacious, safe, cheap and easy-to-apply treatment, which should be considered as first-line therapy for NDM onychomycosis.

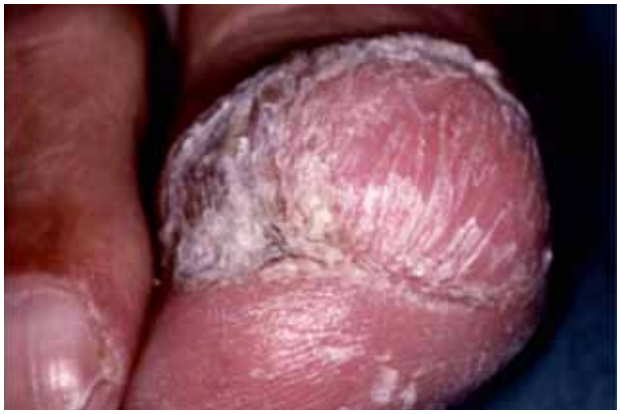

Fig2 - Digital fibromyxoma. © B. Richert

2012 Highlights

Bertrand RICHERT

Chow WT, Bhat W, Magdub S, Orlando A. In situ subungual melanoma: Digit salvaging clearance. J Plast Reconstr Aesthet Surg. 2013; 66: 274-6.

The authors report the case of a 41 year-old Caucasian female with a 4-year history of a longitudinal streak of pigmentation in her great right toenail. An incisional biopsy of the lesion was performed, revealing an acral lentiginous melanoma *in situ*. A multidisciplinary team meeting recommended a further wide excision of the lesion. After marking out a 10mm excision margin around the nail unit, the subungual soft tissue was dissected down to the bone using a scalpel **(Fig 3)**. An oscillating saw with a fine blade was used to excise, parallel to the nail bed, a 1 mm thickness deep layer of bone. This produced a single specimen that could be serially cut to make sure that the melanoma was really *in situ* along the whole extension of the nail bed and germinal matrix. The excision also exposed spongious bone that provided an adequate bed for the skin graft. Histological clearance was achieved and at outpatient follow up, there were no clinical signs of recurrence.

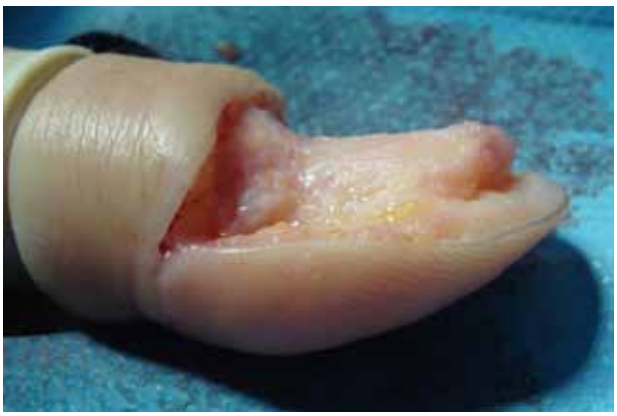

Fig3 - Removal of the nail unit for a *in situ* melanoma. Healing may be obtained by grafting or secondary intention. © B. Richert

COMMENTARY B. RICHERT

Nail cosmetics are still booming. UV gels (also called soak-off gels) appeared after the glue-on plastic nails and the sculptured acrylic nails and nowadays nail-salons apply UVA curing nail polish (e.g. Shellac®). This new nail coating may last up to 3 weeks without developing any visible defect, after which it is removed with a wooden stick, 10 minutes after applying on the coating a cotton pad soaked in acetone. The reason why women are very fond of these techniques using UV is that they are fast, give a glamourous look in a few minutes, are resistant for a long time and require only one session a month. In 2009, one publication reported the cases of two women with a history of UV nail light exposure, who developed squamous cell carcinomas on their dorsal hands. The authors concluded that exposure to UV nail lights is a risk factor in the development of skin cancer.[1] On the basis of historical information and comparisons between UV nail and tanning bed lamp wattages, the authors suggest that UV light emitted from these nail lamps is the cause of these lesions. However, this case review is anecdotal, as no other publication has reported such lesions. Marlova et al claim that the spectral irradiance cannot be calculated by using bulb wattage (the bulb's power requirements) simply exposed to body surface area, but must be measured spectroradiometrically, as performed in their study. They showed that the risk linked to the technique is extremely low. Diffey et al, in another study, used another calculation for determining the relative risk, a simple power law relationship linking risk, annual UV dose and age. They came to the same conclusion, which is that the use of UVA nail lamps use is associated with a very low risk. They also suggest that wearing fingerless gloves would reduce the risk to virtually zero.

Indeed basal cell carcinoma (BCC) is exceptional on the nail apparatus (less than 25 cases published). This might be due to the fact that the nail apparatus is devoid of follicular units and that the physiological position of the hand protects against any sun radiation. Developing two concomitant BCC on two proximal nail folds is very unusual and was the first case ever reported. The first idea was to search for some precipitating factors. The patient had no chronic sun exposure and no relevant medical history. Looking for an external cause revealed the application of a nail lacquer made in the Far East that was not submitted to European regulations. The authors suspected that the nail polish contained some toxic chemical. This is highly possible as the lesions on the proximal nail folds developed several months after regular application of the incriminated nail lacquer. However, it can be assumed that this lady was not the only one to

Bertrand RICHERT

apply this brand of nail polish and there have been no other reports of patients developing BCC of the nail fold. It is most probably the conjunction of toxic chemicals and personal predisposition that led to the development of the tumors.

No one can continue to ignore superficial acral fibromyxoma after reading the article from the Harvard Medical School, presented with a very impressive numbers of cases. This entity has to be added to the tumors with nail tropism, such as onychomatricoma. Many pathologists are unaware of it and have mistaken it with neurofibromas or called them "atypical" fibromas. Its clinical presentation is very typical and once a few of them have encountered, the diagnosis will always be suspected.[2] Suggesting the diagnosis to the pathologist is also useful. One should note that all recurring tumors were located at the nail apparatus and resulted from incomplete excision. This location is where surgeons are always fearful of inducing a permanent nail dystrophy and perform a much "lighter" surgical gesture. Incomplete excision is not a problem in this case, as this is a benign tumour.

Dermatophytes are the main cause of onychomycosis, but various non-dermatophyte molds (NDMs) are often the infectious agents in abnormal nails. NDMs account for about 15% of all single-agent onychomycoses **(Fig 4)**.

Current in vitro and clinical data indicate that NDM onychomycosis, in particular, *Fusarium* spp. and other NDMs are mostly insensitive to standard onychomycosis treatment with topical agents as well as to oral terbinafine and itraconazole. The authors recently reported a series of patients in whom multiple classic oral, topical and combined therapies failed to achieve cure and showed that all of these patients were affected by NDM onychomycosis.[3] In vitro studies have amply demonstrated that NDMs, in particular *Acremonium* spp. and *Fusarium* spp., are mostly resistant to itraconazole and terbinafine, while being highly sensitive to amphotericin B. Amphotericin B belongs to the polyene class of antimicrobial compounds, is fungicidal and has a broad antifungal spectrum. In order to enhance ungual penetration, it was formulated in a dimethylsulphoxide solution that is known to enhance ungual permeability to lipophilic substances. This treatment seems very interesting, easy to perform and innocuous. However, reality is a bit different! In Belgium, it is almost impossible to obtain the drug from a local pharmacist and the preparation costs more than 75 euros for the patient, as it is not reimbursed for this condition. In France, it seems to be available from doctors having access to a hospital pharmacy... This could be a very interesting topic for the physicians of various nationalities to discuss at our forthcoming European Nail Society meeting.

Fig4 - Mould onychomycosis. © B. Richert

To see a non-amputative approach concerning the excision of subungual melanoma in situ in a surgical journal is a real pleasure! Indeed there have been only a limited number of series on the subject, mostly in dermatological literature. It is a pity that the authors forgot about the princeps article that initiated this functional surgery:[4] Moehrle et al compared a nail apparatus melanoma treatment outcome in 62 patients, all thicknesses included (Breslow 1 to 4 mm, mean 1.68 mm). 31 cases were treated with conservative "functional" surgery (sometimes removing the most superficial layer on the bony phalanx) and 31 with phalanx amputation. No significant difference in terms of recurrences or survival rate was found between the two groups. Survival rate reached 92% at 5 years.

The case reported in this paper benefited from an incisional biopsy. Nail doctors do not like this approach for melanocytic lesions. Complete removal of the whole pigmented lesion (excisional biopsy) allows adequate histopathological examination, serial cuts and diagnosis **(Fig 5)**. This is one of the reasons that prompted Haneke to develop the tangential excision of a pigmented lesion of the matrix. The authors do not mention the follow up

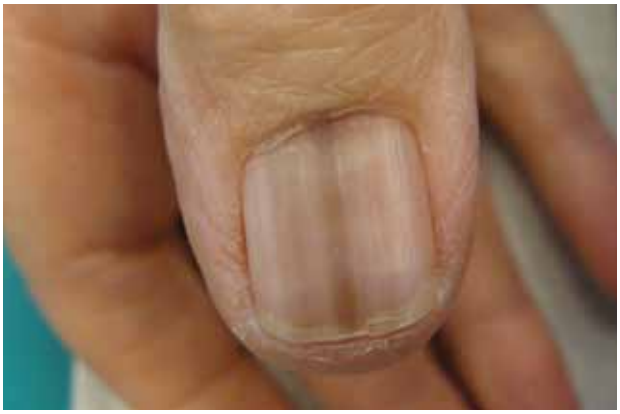

Fig5 - Very suspicious pigmented lesion. © B. Richert

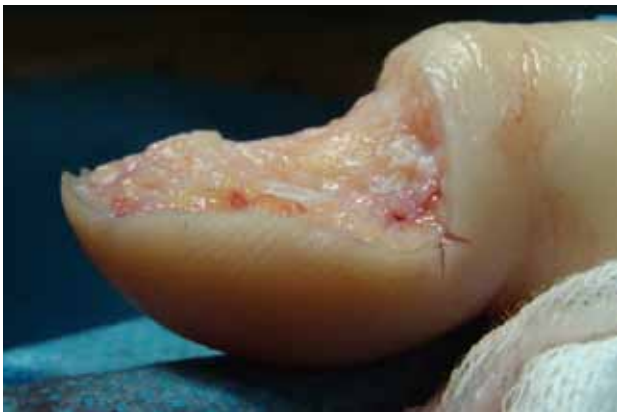

Fig6 - Removal of the whole nail apparatus with 6 mm margins. © B. Richert

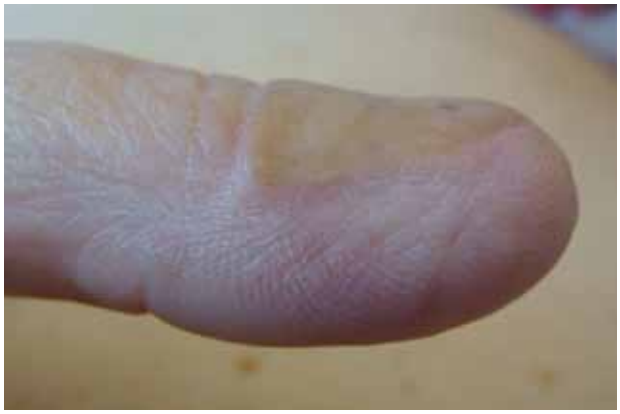

Fig7 - Histology showed melanoma in situ on serial sections. Grafting then was performed. One year post op aspect. Full function is preserved and cosmetic aspect is very acceptable. © B. Richert

time. We recently demonstrated that recurrences may occur later (> 10 years) and that regular follow-ups are mandatory.[5]

Although several studies have been reported on the management of subungual melanoma *in situ*, there is currently no agreed consensus regarding the optimal operative approach for the treatment of this condition. The revised 2010 UK guidelines for the management of melanoma recommend a 5 mm surgical excision margin for melanoma in situ to achieve complete histological excision. The limiting factor of a subungual melanoma, compared with a cutaneous one, is the difficulty in achieving clearance at the deep margin, whilst trying to lift the specimen in a subperiosteal plane without fragmenting the tumor **(Fig 6)**. The new technique reported here allows easier control of the deep plane and most importantly produces a specimen that can be orientated and serially cut by the pathologist to ascertain that there are no areas of invasion. This surgical approach, when used in the setting of melanoma *in situ*, also allows preservation of toe length, which is important for weight-bearing and provides a cosmetically acceptable outcome **(Fig 7)**. We sincerely hope that this paper will be read by a vast number of our surgical colleagues!

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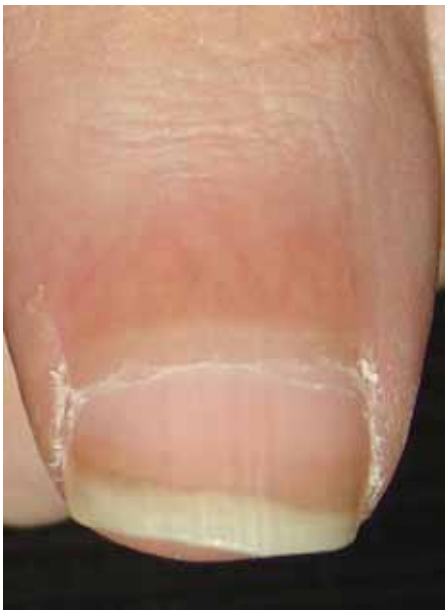
The nail - What's new ? n°6

Clinical Cases

Clinical case from R. BARAN, MG. TURKMANI and T. MUBKI



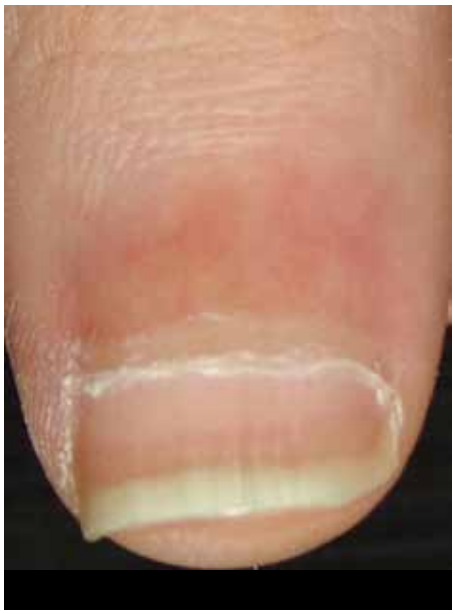


Fig1 & 2 - Acquired racquet nail of both thumbs. © R. Baran, MG Turkmani & T. Mubki

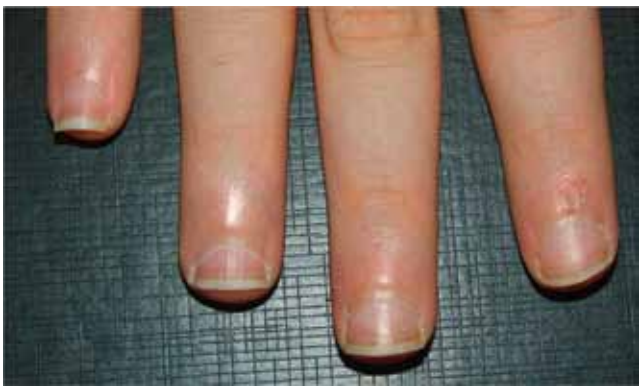


Fig3 - Shortness of the nail bed sparing the 5th finger.
© R. Baran, MG Turkmani & T. Mubki

A 20 y.o. healthy male presented to our clinic with a 2 year history of asymptomatic changes of the shape of all finger nails. The patient reported no family history of the same complaint. Physical examination showed widening and shortening of all finger nails bilaterally with the exception of little finger nails **(Figs 1-3)**. Toenails were spared. Plain x-ray of both hands showed low bone density in the proximal phalanges in the 2nd to 5th finger bilaterally. Blood tests showed high parathormone (PTH) (110.3pg/ml; reference range: 15-85), serum 25-hydroxy-D3 was low (< 10.0nmol/L; reference range >=75); TSH, T3, T4, calcium, phosphorous and creatinine were within normal limits.

What is your diagnosis?

Robert BARAN

The diagnosis of acquired racquet nails (brachyonychia) in association with hyperparathyroidism was established. There are very few cases of hyperparathyroidism published in the literature.[1,3] In our observation, besides the high level of PTH it was easy to rule out psoriatic arthropathy with ultrasonography and X-ray. Absence of nail biting was obvious. It is customary to distinguish three categories of hyperparathyroidism. In primary type (the most common), there is usually autonomous secretion of PTH by a single parathyroid adenoma (90%), while carcinoma has been reported vey rarely (1%). Secondary hyperparathyroidism is present when there is hyperplasia with increased PTH reaction in an attempt to compensate for a prolonged hypocalcemia. Its effect is to restore serum calcium levels. This type is usually due to chronic renal failure, malabsorption, osteomalacia and rickets. In a very small proportion of cases of secondary hyperparathyroidism, continuous stimulation of the parathyroid glands may result in adenoma formation and autonomous PTH secretion. Definition of tertiary hyperparathyroidism is a primary hyperparathyroidism developed on a hyperparathyroidism that is secondary to a hypocalcemia of a renal insufficiency. From a diagnostic point of view it is easy to recognize because it is a hyperparathyroidism during a renal insufficiency which is no longer in hypo or normocalcemia, but results in a hypercalcemia.

Radiographically, racquet nails can be associated with some characteristic changes. In early stages, subperiosteal demineralization can be noted in the phalanges. This may be followed by resorption of the terminal phalanges with occasional appearance of acroosteolysis. This is particularly true in "brown tumor" of hyperparathyroidism which can be indistinguishable from giant cell bone tumor and giant cell reparative granuloma of the bone upon pathologic analysis.[4] Beside the racquet nails, cyanosis of the finger tips as a result of decreased perfusion from vascular calcification may lead to gangrene of the fingers and toes. Onycholysis, pachyonychia, Muehrcke's bands, leuconychia, half-and-half nails and koilonychia may also be associated with nail changes.

In conclusion, we recommend measuring parthormone and serum 25 hydroxy-D3 in every patient with an acquired form of racquet nails.

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Clinical case from Véronique BLATIÈRE

For 7 years this patient **(Fig 1)** was treated for "onychomycosis" including systemic treatment. Her podiatrist regularly filed the thick nail plate, so that it was less painful and she could wear shoes.

What is your diagnosis?

This is a typical case of onychomatricoma as described by Baran and Kint in 1992. The etiology of this filamentous tufted tumor of the nail matrix remains unknown.[1,2]
The clinical features for diagnosis can be seen in Figure 1 **(Fig 1)**:

- presence of a longitudinal yellowish band of varying thickness;
- splinter hemorrhages mostly involving the proximal portion of the nail plate;
- prominent longitudinal ridging associated with a tendency to transverse and longitudinal curvature.

Imaging was necessary to convince our patient that she had a nail matrix tumor and that the only treatment was surgical. Ultrasonographic examination showed a hypoechoic tumoral lesion affecting the matrix zone with hyperechoic linear spots and projections into the interplate nail space **(Fig 2)**.[3]
MRI showed finger-like projections emerging from the nail matrix, both with and without gadalinium **(Figs 2 - 4), (Figs 3a,b)**.
Distal nail clipping was not performed.[4]
Under local anesthesia and light sedation, a tourniquet was placed, the proximal nail fold was incised and the nail plate avulsed, revealing the filamentous digitations. The tumor was carefully dissected from the matrix **(Fig 4)**. An artificial nail plate was tailored from an infusion foil **(Fig 5)** in order to avoid adherence from the ventral surface of the proximal nail fold to the freshly injured matrix.[5] This would have led to a complication called pterygium. The pathology report confirmed the diagnosis **(Fig 6)**.[6] Normal nail regrowth was observed **(Fig 7)**.
This clinical case is of interest because the onychomatricoma was large and was misdiagnosed for a long time and erroneously treated as onychomycosis.

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Fig1 - Clinical feature. © V. Blatière

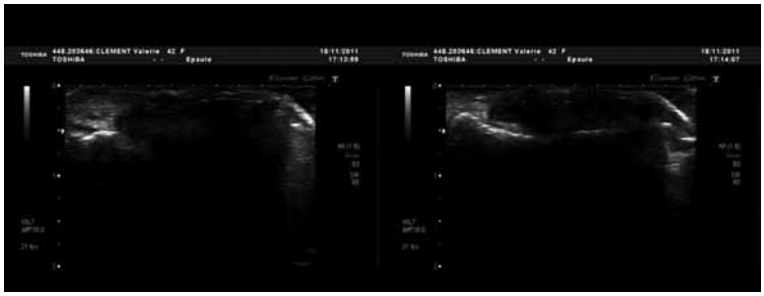

Fig2 - Ultrasonography. Hypoechoic mass with linear projection. © Dr E. Terqueux, Montpellier, France

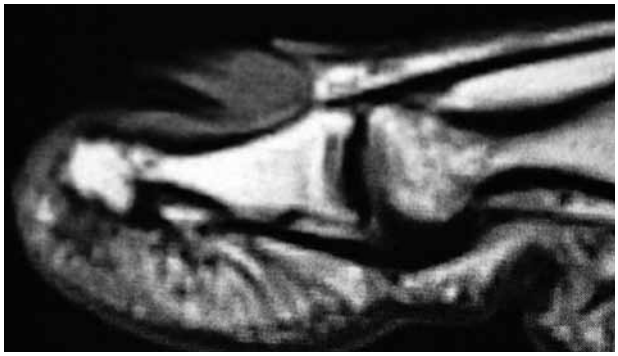

Fig3a - MRI of the nail unit. T1. Sagittal view: Finger-like projections. © Dr E. Terqueux, Montpellier, France

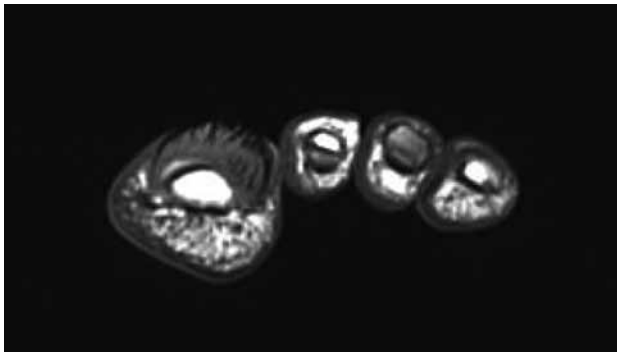

Fig3b - MRI of the nail unit. T1 with gadalinium. Frontal view: Finger-like projections. © Dr E. Terqueux, Montpellier, France

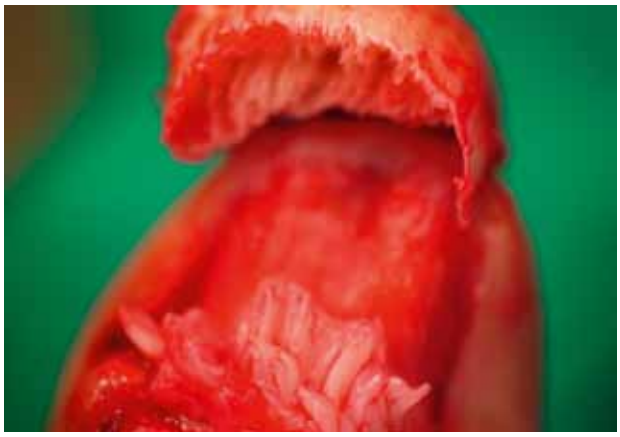

Fig4 - Per-op view. The thick nail plate is perforated by "woodworm-like holes". The filamentous tumor exhibits multiple "glove-finger" digitations. © V. Blatière

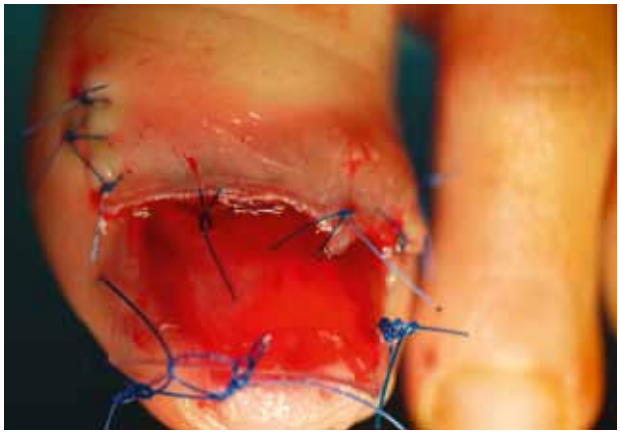

Fig5 - A nail substitute. © V. Blatière

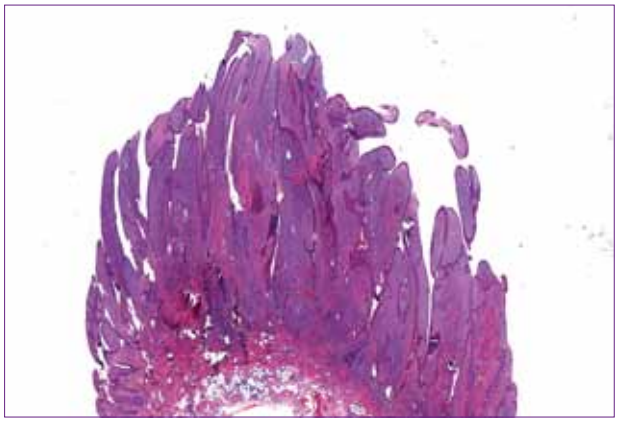

Fig6 - Histologically, onychomatricoma is a fibroepithelial tumor of the nail matrix that presents as characteristic epithelial digitations in the nail plate. © Dr L. Durand Montpellier, France

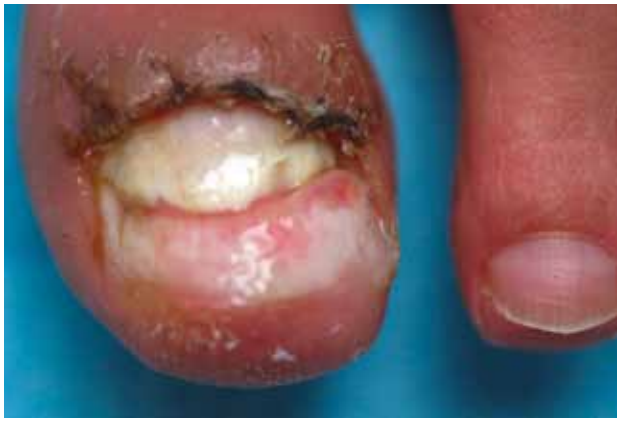

Fig7 - 3 months post operatively. © V. Blatière

Clinical case from Osvaldo CORREIA

Fig1 - Nail dystrophy of both thumbs. Periungueal inflammation of the first three fingers of both hands. © O. Correia

A 45 years old man,working as an engineer, came to our consultation for a long-lasting nail dystrophy of both thumbs, associated with inflammation of the skin of the proximal and lateral nailfolds. He reported previous treatments with different topical and oral antibacterial and antifungal drugs without improvement.
The clinical examination of the fingernails revealed a prominent pigmented longitudinal central depression of both thumbnails, associated with periungueal inflammation of the first three fingers of both hands **(Figs1 & 2)**.
The patient was in good health, denied any current oral or topical treatments and complained that the thumbnails had not been growing for several months.

What is your diagnosis?

Osvaldo CORREIA

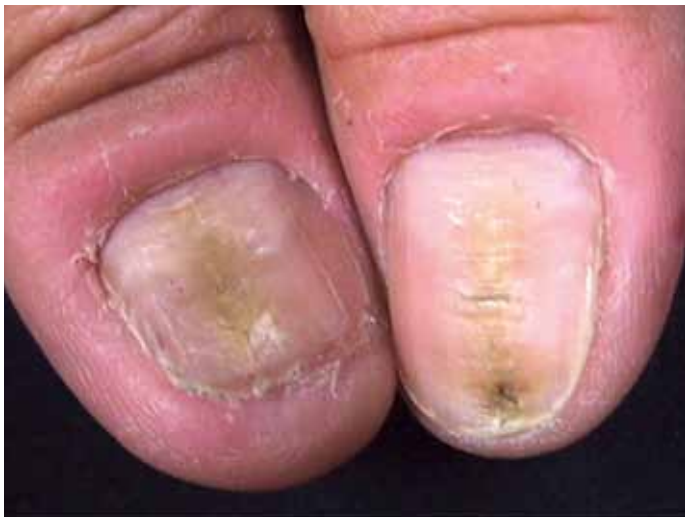

Fig2 - Close up of the nail dystrophy of both thumbs. © O. Correia

The clinical diagnosis was Onychotillomania.
The thumbnail plates show a median canaliform nail dystrophy presenting as a pigmented and severe longitudinal central depression. It is also possible to see some discontinued Beau´s lines associated with inflammation of the skin of the proximal, lateral and distal nailfolds in both thumbnail plates. Periungual inflammation of the first three fingers of both hands was also present. Patients usually have the habit of chewing or biting the periungual tissues, and this can give rise to acute or chronic paronychia and sometimes longitudinal melanonychia. The median canaliform nail dystrophy is due to the habit of rubbing and pushing back the mid-portion of the cuticle of the thumb with the adjacent index finger. This usually occurs in nervous or anxious people, who often have a history of nail biting.
The treatment is continuous bandaging during the day and hand moisturizing cream at night, with massaging of the nails from the proximal to distal area to minimize the loss of cuticle. Detailed explanations are given to the patient on the reasons for the nail dystrophy and the need for prolonged treatment with occlusion and eviction of trauma.
Patients are often misdiagnosed for other diseases like onychomycosis, bacterial infection, psoriasis or lichen planus.[1,2]
Onychophagia may promote longitudinal melanonychia.[3,4]

Onychotillomania can present under many different guises, the most frequent being onychophagia, or nail biting, more common in children and sometimes with family association. Adult patients may use various tools (such as scissors, knife, toothpick...), and in these cases onychotilllomania can be associated with obsessive compulsive disorder.[5]
These patients may improve with the help of behavioural therapy, serotonin re-uptake inhibitor drugs and psychiatric help.

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Clinical case from David DE BERKER

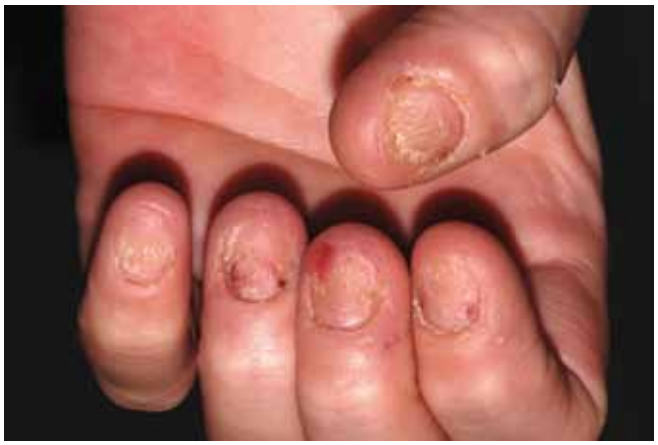

Fig1 - The nail plate is lost and there are erosions, small haemorrhages in the nail folds and splinter haemorrhages in the nail bed. © D. D Berker

A 32 year old male office worker presented with disease of all his fingernails. There was a history of an injury to the left index finger and thumb three years previously and the nails on the left hand had gone on to all develop the same problem with gradual disintegration and loss of all nails. Within 12 months the problem had extended to the right hand with similar changes **(Fig 1)**. Initial clippings for mycology had been negative and after 12 months, there was no nail to sample. Treatment with potent topical steroid and protective measures had not been helpful.

There was no history of other skin problems and the patient was well. In addition to office work, he had hobbies of making wooden models which entailed the use of glues. Examination revealed the same changes on both hands and no changes on the toes. There was scaling of the nail bed and nail folds with haemorrhage scattered within the same structures. There were focal erosions. Close examination of the exposed nail bed revealed splinter haemorrhages. There was no change elsewhere on the skin or in the mouth or genitals.

Scraping from the scaled areas again failed to grow any fungi. The differential diagnosis lay between onychomycosis, lichen planus, allergic contact sensitivity and trauma. A lateral longitudinal nail biopsy was undertaken to help differentiate between these. The result showed hyperplasia of the nail bed, patchy mixed inflammatory infiltrate but no spongiosis, keratinocyte death or civatte bodies. There was a small focus of haemorrhage in the papillary dermis. There were no fungi on special stains.

What is your diagnosis?

David DE BERKER

The histology was consistent with trauma and led to a more detailed enquiry about the pattern of evolution of the disease. It became clear that the patient noted small spurs of nail growing from the damaged nail unit and in order to prevent "catching" the nail, he would bite off the spur of nail. This gradually became a regular evening activity in order to make the nails more tidy. Whilst it was based on the original focus of trauma, it became a more generalized pattern of nail biting, but at no point extended to the toes. This pattern of onychophagia is reasonably typical and can have the differential described in this instance. It is also sometimes seen in combination with a second pathology which acts as the precipitating abnormality, but which in time becomes hidden or displaced by aggressive nail biting. The clinical features in favour of onychophagia as a diagnosis were the mixture of haemorrhages and erosions and also the exclusion of the toenails. Lichen planus would have been likely to affect toenails as well. Although an allergic contact sensitivity was possible given the difference between fingers and toes, the pattern of onset, the marked loss and the histology were all against it. Onychomycosis remained a possibility and can cause this pattern of fingernail loss, but the negative mycology of both clippings and scrape and subsequently no fungi on histology, makes this very unlikely. The final observation that helps conclude the diagnosis is the post-operative course. During the 6 weeks following the biopsy, the sampled digit was tender and dressed much of the time. This prevented the previous habit of biting and in this interval, nail growth began to normalize. This helped both clinician and patient recognize the diagnosis and plan preventive therapy. Initially, treatment was by binding the ends of three chosen digits with paper surgical tape throughout the day and night for 10 weeks. This was with the aim of both protecting the digits and reminding the patient of his tendency to chew. Medication can sometimes be tried in self injurious nail diseases[1] and there may be psychological factors that need to be addressed.[2] However, there is no substitute for a lateral longitudinal nail biopsy[3] when you want to establish a clear diagnosis that is acknowledged by both the patient and the clinician.

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Clinical case from Bruno FOUILLOUX

A 57-year-old woman came to our consultation for a perionyxis which had persisted on her left big toenail for three months.
The clinical examination showed an indolent erythematous papule at the proximal angle of the external lateral fold and an important swelling of the proximal nail fold **(Fig 1)**.

Fig1 - Clinical aspect : perionyxis with an erythematous papule of the lateral nail fold. © B. Fouilloux

What is your diagnosis?

Even if such an inflammatory aspect of the perionychium is unusual for a tumor, a carcinoma should be excluded. A foreign body reaction must be evoked, although the patient did not report any trauma. The lesion was too limited for a retronychia.
On radiological examination, there was no morphological or structural abnormality. The articular space was respected. We noted only a little calcification on the external side of the second phalanx of the left big toenail **(Fig 2)**.

MRI showed neither abnormality of the nail bed, nor of the underlying tissues. However, an important inflammation (58 mm thick) of the external side of the lateral nail fold was observed **(Fig 3)**.The contrast MRI enhancement was similar to that observed in glomic tumours or haemangiomas, but the morphology was incompatible with these two hypotheses. Before surgical removal, we suspected either an atypical ingrowing nail or a pyogenic granuloma of undetermined origin, or even an atypical haemangioma, a carcinoma, a sarcoma or a lymphoma.
During the surgical removal of the lesion, we found a not well circumscribed, fibrous and keratinous tumor, more or less adherent to underlying bone. The complete excision of the lesion was rather difficult.

Histopathological analysis **(Fig 4)** showed a focus of orthoplasic osseous metaplasia with edematous change and ulceration on the surface. There was no tumoral proliferation. The analysis concluded that it was an atypical exostosis. Subungual exostoses are outgrowths of normal bone or calcified cartilaginous remains. These lesions arise from the distal phalanx beneath the nail. They are not uncommon, but are underdiagnosed and not reported often enough. The clinical aspect can mimic warts, fibromas or ingrowing nails. Recently Bettioui described a subungual exostose mimicking a keratoacanthoma.[1] Exostoses are usually painful, are as hard as stones and may elevate the nail.
They are most frequent in young people and especially on the big toenail.
Trauma appears to be a major causative factor, though some authors do not agree with this hypothesis.
The triad consisting of pain-nail deformation and radiographic features enable to evoke the diagnosis.
On radiography, exostosis appears like an ill-defined trabeculated osseous growth with an expanded distal portion covered with fibrocartilage.

Lemont and Christian[2] suggested a new classification of subungual exostoses, in genetic and acquired types. The classification was based on the histopathological aspect, the radiographic appearance, the location of the lesion and the patient's age.
Dermoscopy shows a well-circumscribed yellowish round or ovoid lesion.
MRI is not usually necessary for diagnosis. However, it is the best radiologic modality able to depict the effect of subungual exostosis on surrounding structures and to distinguish this lesion from osteochondroma. It allows to recognize hyaline cartilage from fibrocartilage. The fibrocartilaginous cap in subungual exostosis is hypointense with all MRI imaging sequences, whereas the hyaline cartilage in osteochondroma has a high signal intensity on T2-weighted images.[3] MRI is mainly indicated for the diagnosis of a purely radiolucent cartilaginous exostosis.

Bruno FOUILLOUX

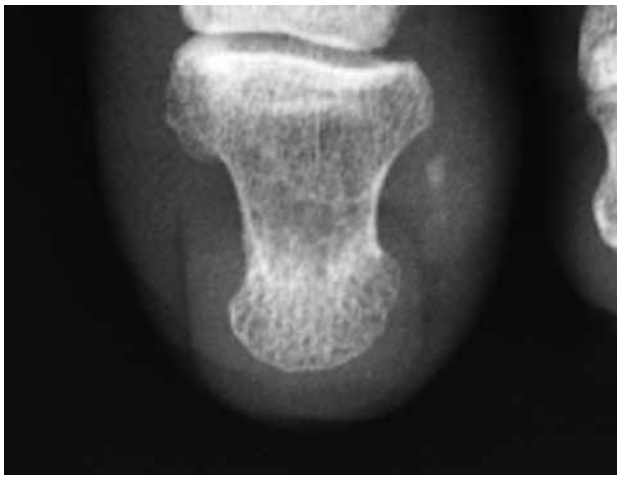

Fig2 - X ray showing a calcification on the external side of the second phalanx. © B. Fouilloux

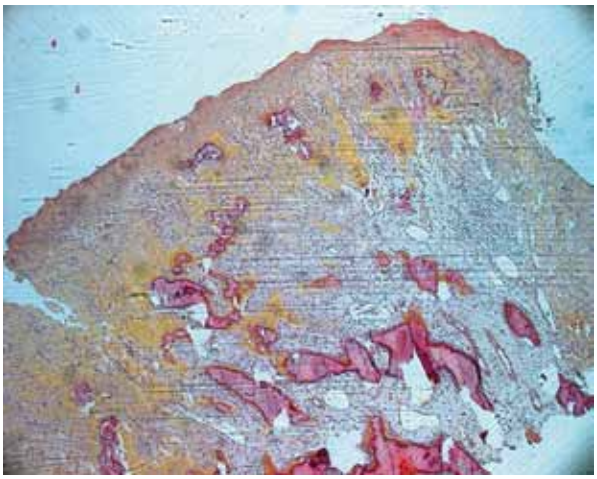

Fig3 - MRI showing important inflammation. © M.Cuilleron

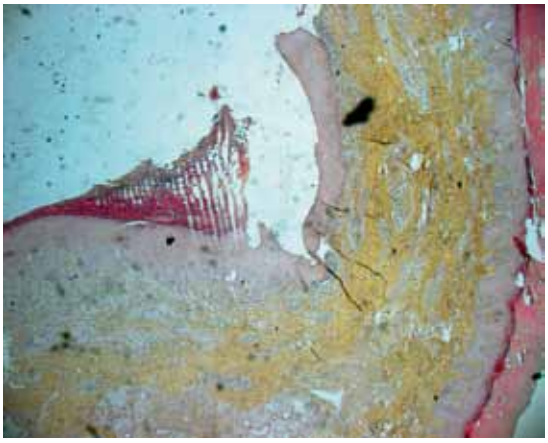

Fig4 - Histopathology showing osseous metaplasia. © C.Douché

Histologic examination shows a proliferative fibrocartilaginous cap that merges into hyaline cartilage forming mature trabecular bone at its base by enchondral ossification.
Sometimes relapses occur after surgical removal. De Berker reported 10% of relapses in a study of 21 patients.
Our clinical case shows an atypical clinical aspect of periungual exostosis with chronic perionyxis and pyogenic granulomas-like lesion. Radiological examination showed a small calcification. Neither MRI, nor the clinical aspect during surgery helped us to make the diagnosis. Only the histopathological exam was able to confirm the diagnosis.
With specials thanks to Dr Josette ANDRE (Bruxelles).

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Clinical case from Eckart HANEKE

A 34-year-old immigrant African Black patient living and working in the south of Switzerland was referred to our department because of a black thumb nail. He had been employed as a kitchen help in a restaurant and had repeatedly injured his hands with both heat and heavy items. After he had jammed his right thumb 5 years ago his nail never grew normally again. He noticed a gradual darkening of his thumb nail and a distal onycholysis, which developed into a short nail with some distal nail bed hyperkeratosis. His referring dermatologist's suspected diagnosis was subungual melanoma because of the localization on the thumb, the history of a previous trauma and the slow and insidious development.
At consultation, he reported no relevant diseases in his personal and family history. A fungal examination had been negative. He was otherwise healthy except for the distress caused by the fear of having a malignant lesion. There was no sign of skin or nail infections. The thumb nail was diffusely dark brown with even darker pigmentation of the skin of the proximal nail fold. The lunula was virtually black **(Fig 1)**. Dermatoscopy showed hyperpigmentation of the nail with some visible, but ill-defined banding.
Because of his history and the patient's insistence, the mycological examinations were repeated and a lateral longitudinal biopsy was performed.
Mycology did not grow a dermatophyte. Histopathology confirmed the clinical diagnosis of an onychomycosis. In H&E stained sections, there was a slightly thickened, but short nail plate **(Fig 2)**. There was an enormous orthokeratotic nail bed hyperkeratosis with moderate papillomatosis of the epithelium **(Fig 3)**. Spongiform pustules were seen in middle between the proximal tip of the matrix and the lunula **(Figs 4-6)**. Elsewhere, some neutrophils were seen in the hyperkeratosis, and some Munro's microabscesses. A dense lymphocytic infiltrate was observed under the spongiform pustule, but otherwise there was only a moderate, predominantly perivascular lymphocytic infiltrate in the upper dermis.
PAS showed long slender hyphae arranged both in parallel to the growth direction of the nail and also vertically that invaded the distal matrix as well as the undersurface of the nail plate over the spongiform pustules **(Figs 7,8)**. The nail bed hyperkeratosis was virtually free of fungal elements. Melanin granules were detected in the proximal matrix just distal to its beginning and increased in number distally. Close to the inflammation under the spongiform pustule, melanocytes with long dendrites were seen. Melanin granules were seen in the nail plate, but not in the nail bed hyperkeratosis. There were no intraungual melanocytes. A diffuse yellow-brown stain of the nail as seen in onychomycosis nigricans was not present.
A combined topical and systemic antifungal treatment was recommended.

What is your diagnosis?

Melanomas are rare in dark-skinned individuals, but most of them occur in acral locations, particularly on the soles of the feet and more than 20% in the nail unit. The thumb and big toe nails are the most frequently affected nails. Previous trauma was repeatedly reported. The proximal nail fold's hyperpigmentation in our patient though with gradual merging with the adjacent skin was seen as a potential Hutchinson's sign. Therefore, the suspicion of a subungual melanoma was justified. Unfortunately, it is often the other way: a subungual melanoma is mistaken for onychomycosis for a very long time, frequently with fatal consequences.
On the other hand, virtually all irritations such as trauma, inflammation or a tumor may cause nail pigmentation in persons with dark complexion. Nail bed hyperkeratosis and a short, broken nail may occur in a variety of conditions, both melanoma and onychomycosis included. However, our clinical diagnosis tended more to onychomycosis and therefore a diagnostic lateral longitudinal nail biopsy was discussed with the patient and then performed. Single-digit onychomycosis could be confirmed.
In recent years, we have seen more than a dozen patients with single-digit onychomycosis none of whom had been diagnosed correctly as a fungal nail infection. Previous mycological cultures had either been negative or the cultured fungus was not unanimously accepted as a nail pathogen. All patients had a moderate to severe trauma to the digit and all but one patient had only one finger nail affected, the other had a single toe nail involved. No mycosis of the surrounding skin was found. Thus we believe that post-traumatic single-digit onychomycosis is a particular (sub)entity and should be searched for in case of onychodystrophy of a single nail, particularly in young to middle-aged individuals.

Eckart HANEKE

Fig1 - The right thumb nail was dark brown to black and proximal nail fold was also much darker than the surrounding skin. © E. Haneke

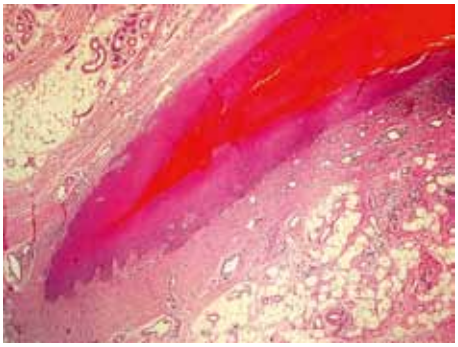


Fig2 - Medium power microphotograph of the matrix region showing a spongiform pustule. © E. Haneke

Fig3 - Marked orthokeratotic hyperkeratosis of the nail bed. © E. Haneke

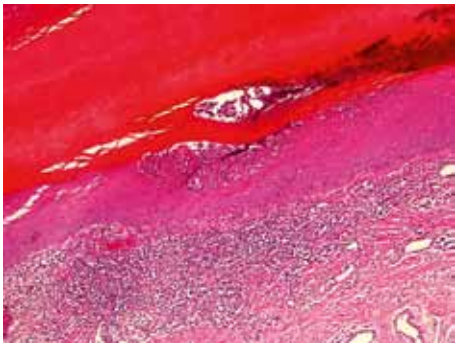


Fig4 - Higher maginification of the spongiform pustule demonstrating a dense inflammatory infiltrate in the upper dermis. © E. Haneke

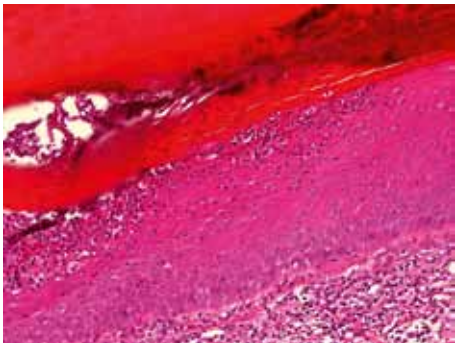


Fig5 - This microphotograph shows the psoriasiform spongiform invasion of the distal matrix b neutrophil granulocytes. © E. Haneke

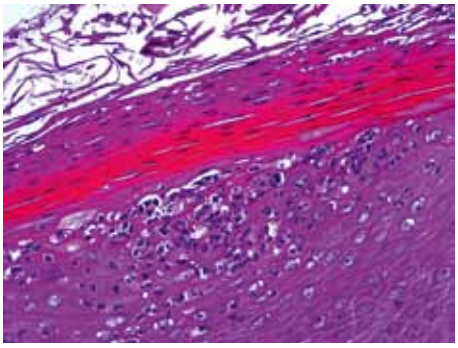


Fig6 - Close-up of the spongiform pustule and the overlying parakeratosis, which is less compact in its upper layers and exhibits oval spaces where the fungi are. © E. Haneke

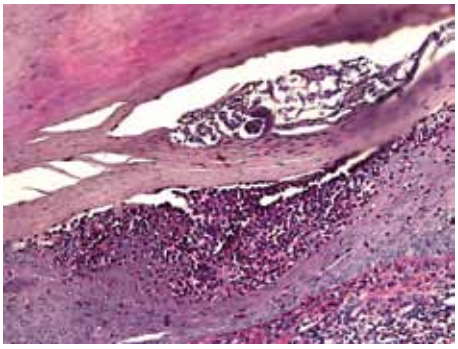


Fig7 - PAS stain reveals fungal hyphae. © E. Haneke

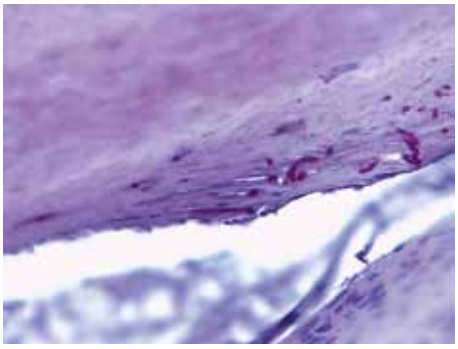
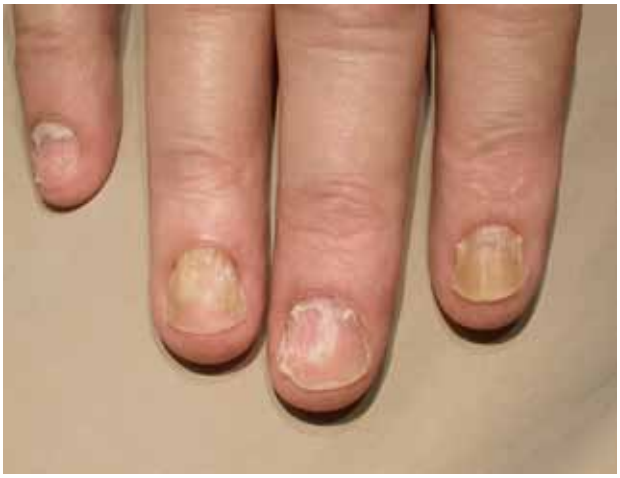
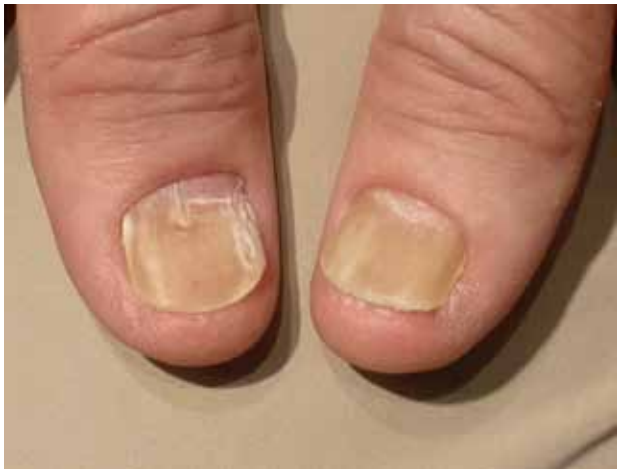


Fig8 - Hyphae are almost exclusively present over the spongiform pustule. © E. Haneke

Clinical case from Jose Maria MASCARO





Figs 1 & 2 - A 64 year old man with a thymoma developed twenty nail alterations (trachyonychia, longitudinal ridging, onycholysis). © JM. Mascaro

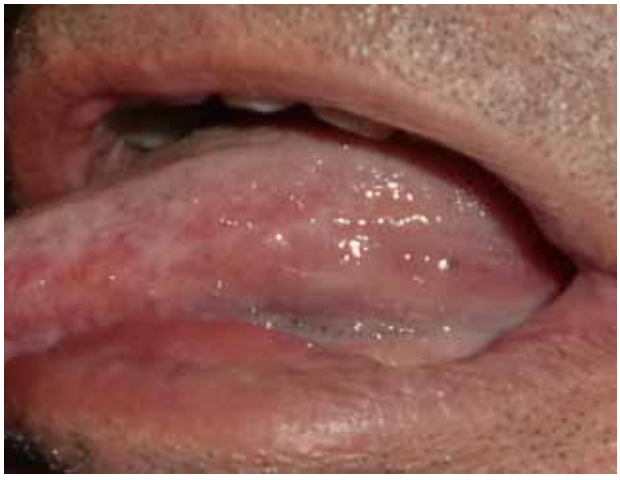


Fig3 - Dermatological inspection permitted to note a slight whitish reticulate on both lateral borders of the tongue and oral retrocomisural areas. © JM. Mascaro

A 64 year old man consulted in July 2012 for twenty nail alterations that had progressively developed over the previous two years. As a relevant medical antecedent he pointed out that 18 months before he had suffered from severe respiratory problems; after complete examination it was found he had a thymoma that was fully removed in September 2013.

At the clinical examination all twenty nails presented variable degrees of trachyonychia with longitudinal ridging. Incipient onycholysis and onychomadesis was present in some nails **(Figs 1 & 2)**. General dermatological inspection revealed slight whitish lacy platches on both lateral aspects of the tongue and retrocomisural areas **(Fig 3)**. Two months later the nails, that at the first consultation had shown an early onychomadesis. Oral reticulate leukokeratosis persisted. The patient did not accept nail biopsy.

What is your diagnosis?

Jose Maria MASCARO

Although without nail biopsy, it is not possible to positively confirm the diagnosis of lichen planus, clinical features (trachyonychia, longitudinal ridging) are quite characteristic and concomitant oral mucosa reticulate leukokeratosis supports this hypothesis.

Lichen planus (LP) appears to be an immune mediated inflammatory reaction more than a single disease. In the last decades it has been found that LP is often associated to a large number of diseases and agents, such as viral infections (particularly hepatitis C), auto-immune disorders, drug intake, oral contact with metallic dental restorative materials and a long list of conditions. Clinical manifestations of LP on the skin, mucous membrane and appendages (nails and hair follicule) have diverse clinical forms (i.e. erosive, cicatricial and others). On the other hand, the underlying medical background is variable and, for this reason, dermatologists are familiar with two terms: "idiopathic LP" and "lichenoid reactions" (LR). These last ones include all processes with muco-cutaneous manifestations and microscopical patterns of dense subepithelial lymphocytic infiltrate producing basal cell damage, identical to idiopathic LP, but associated to diverse diseases or agents. Graft versus host disease (GVHD), where alloreactive T cells recognize major histocompatible complex (MHC) molecules of host targeted keratinocytes, is one of the most characteristic examples of LR. There are also other auto-immune diseases where LR appears as a typical symptom, as in paraneoplastic pemphigus. Therefore LP/LR must be taken into consideration for it is possibly associated to an underlying neoplasm.

In the last decades association of thymoma and dermatological disorders, particularly those having a cell mediated immune mechanism, has been reported.[1,4] In 1987 Gibson and Muller[2] referred two cases of LP, 2 of pemphigus and 1 with a LE-like disease in patients with thymoma. And it is interesting to note that in their cases, as in ours, thymectomy did not alter the clinical course of cutaneous diseases. Other associations to thymoma are myastenia gravis[3,4] and medular aplasia.

Hayashi, Shiono and Okumura, in 2008,[1] reported 20 cases of LP associated to thymoma. But out of 227 cases with this tumor seen in their institute since 1997, only one had LP. More recently there have been diverse reports of LP associated to Goods syndrome (hypogammaglobulinemia, acquired combined T and B-cell immunodeficiency and thymoma).[5,7] In one of these patients oral LP lesions improved after tumor resection[5] but this seems to be an exception taking into consideration the usual course in most cases.

The present case is relevant due to LP/LR nail manifestations concurrent with thymoma. Nail alterations were not mentioned as being present in most cases reported with this association.

A study of associated immunologic disorders in patients with "lichenoid" (LP and LR) nail alterations would certainly be interesting. Due to the scarce number of concurrent nail LP/LR and thymoma cases reported (as well as the fact that nails are probably not systematically examined in these patients), it appears useful to publish all the observations that doctors have noticed.

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Clinical case from Bianca Maria PIRACCINI

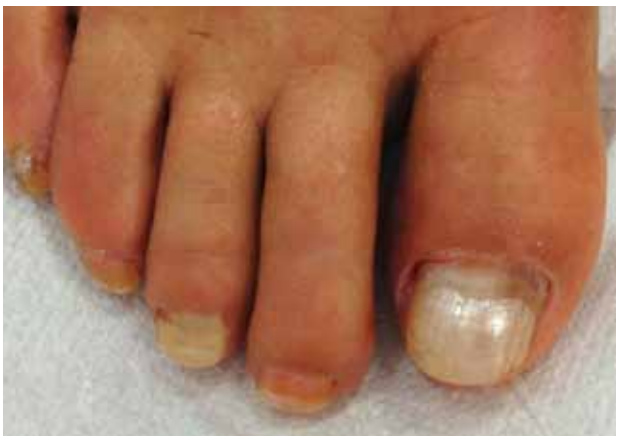

Fig1 - The great toenail of the patient shows subungual red brown discoloration. © BM. Piraccini

A 68-year-old woman under paclitaxel for breast carcinoma was ending her last cycle of chemotherapy when she noticed a black nail discoloration of the first right great toenail. The latter had gradually turned to a yellow-red color and was slightly painful. On the morning of our observation the patient had just noticed the presence of multiple white subungual moving masses not associated with any symptom, under the same great toenail.
The clinical examination of the 1st right great toe showed an onycholytic nail plate of a red-brown color, which was barely visible since the nail was covered with nail polish **(Fig 1)**. Clipping away the detached nail plate revealed an eroded nail bed with some larvae sneaking out from under the remnant of the nail plate **(Fig 2)**. We extracted 11 larvae from the subungual space **(Fig 3)**.

What is your diagnosis?

Taxane-induced acute onycholysis due to nail bed toxicity, infested by sarcophagid larvae of Lucilia sericata.
Acute painful onycholysis, sometimes associated with purulent discharge, is a well-known side effect of taxanes, affecting up to 44% of patients.[1] Nail changes especially due to docetaxel, are dose-dependent and vary in severity from one patient to another. In most cases, after 2, 3 treatment cycles, the patient experiences acute pain of the distal digit followed by the reddening of one or several nails. This precedes onycholysis.
Frequent complications of taxane-induced onycholysis include hemorrhages, due to drug-induced nail bed vessel damage and thrombocytopenia, and bacterial infections. The latter is suggested by the appearance of a purulent discharge from the subungual space, associated with inflammatory signs and severe pain, and requires systemic antibiotics.
Our patient suffered from taxane-induced onycholysis for which she had not asked advice as it was not painful. She had not clipped away the onycholytic nail plate, as she preferred to keep the nail long in order to wear nail polish. The maintenance of the detached nail plate produced a niche where the hemorrhagic and necrotic debris of the nail bed remained and was infested by fly maggots.
Myiasis is an ectoparasitic infestation of living human and other animal tissues by fly maggots (*Diptera*) sustaining from necrotic tissues, which are responsible for semi-specific or opportunistic infestation Cutaneous myiasis may present as furoncular, migratory and wound myiasis.[2] Wound myiasis is the most common form of cutaneous myiasis and occurs worldwide. The flies responsible for this are those of the *Calliphoridae* and *Sarcophagidae* families. The main local factors conditioning the deposition of fly eggs are open wounds or ulcers with smelly discharge from bacterial contamination, necrotic areas and sometimes eroded tumors, such as squamous cell carcinomas. Other predisposing factors include precarious hygiene, poor social conditions, low educational level, psychiatric illness, alcoholism, diabetes, vascular occlusive diseases, physical handicap and advanced age. The larvae may be deposited in mucous membranes and body

Bianca Maria PIRACCINI

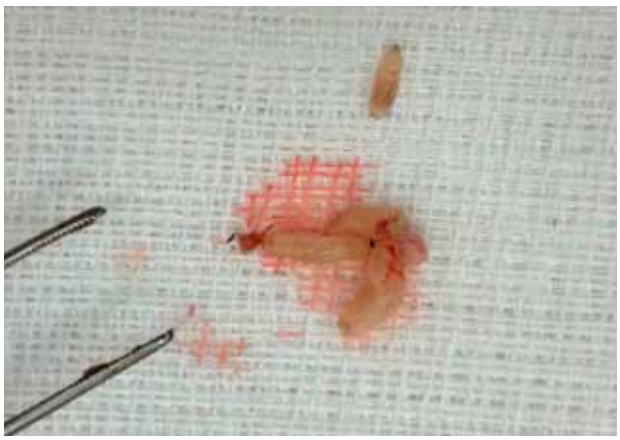

Fig2 - Maggots extracted from the subungual space. © BM. Piraccini

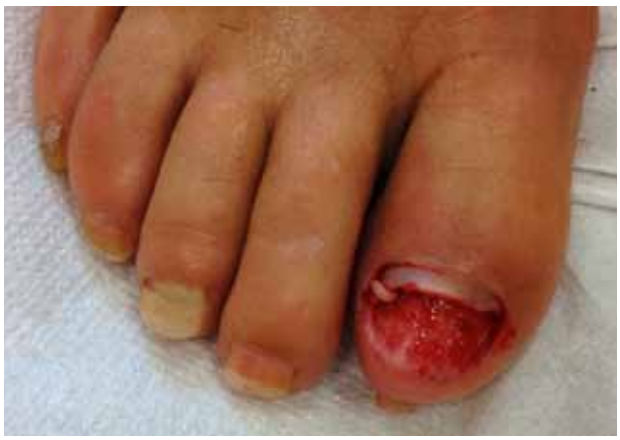

Fig3 - Removal of the onycholytic nail plate shows an eroded nail bed with some larvae emerging from the remnant of the nail. © BM. Piraccini

cavity open lesions, but the most common sites of infestation are chronic leg ulcers of the elderly.

Subungual location is a very rare occurrence of myiasis that requires onycholysis and tissue damage. Only four cases have been reported in literature. In 1978, Munyion et al. reported the first case of subungual myiasis developed after a trauma with consequent subungual hematoma.[3] In 2000, Garcìa-Doval et al. reported a 90-year-old woman with subungual myiasis favored by diabetes and limb ischemia with skin erosions.[4] In 2008, 2 cases were reported: one by Dagci et al., in the great toenail of a patient affected by skin psoriasis undergoing therapy with biologicals[5] and one by Balcioğlu et al. in the great toenail in a 65-year-old patient with severe psychiatric disturbance, lack of personal hygiene and concomitant onychomycosis due to *Trichophyton rubrum*.[6] Onycholysis due to different causes was indeed present in all cases of subungual myiasis reported in literature, as it was in our patient.

Onycholysis describes the detachment of the nail plate from the nail bed. The most common line of cleavage is the nail bed horny layer: this occurs in onycholysis due to trauma, psoriasis and onychomycosis. In these cases, the nail bed epithelium is intact and only shows a reactive hyperkeratosis. In drug-induced onycholysis, especially when due to taxanes, the cleavage results from acute damage to the nail bed epithelium, with nail bed erosion and oozing. If the onycholytic nail plate remains in place, it leads to the formation of a subungual scab where water and organic and inorganic contaminants may remain for a long time. An eroded surface is easily colonized by bacteria: this explains the frequent purulent evolution of taxane-induced onycholysis. In the same way, a concealed wound may be chosen as a site for egg deposition by a housefly. Therefore, in our case, taxane-induced nail bed erosion without the removal of the nail plate created an optimal habitat for the deposition of the eggs which remained there without any other personal predisposing factor.

Our patient was treated with daily footbaths in an antiseptic solution followed by medication with topical antibiotics and oral amoxicillin (2 g/day) for 5 days. At follow up after 10 days, the nail bed was free from larvae and erosion was partly epithelialized. Topical antibiotics were continued until complete healing of the eroded nail bed.

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Clinical case from Bertrand RICHERT

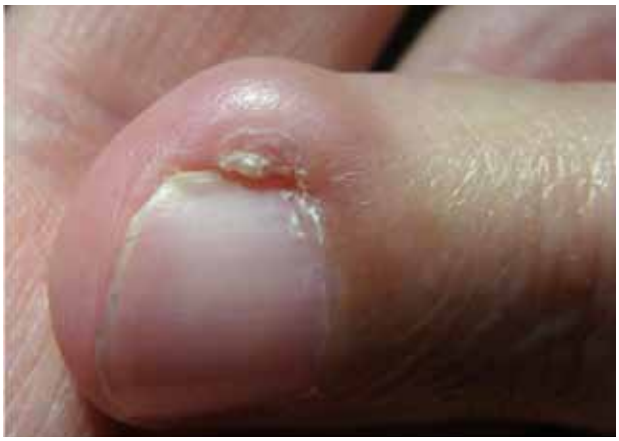

Fig1 - Painless swelling of the lateral wall. © B. Richert

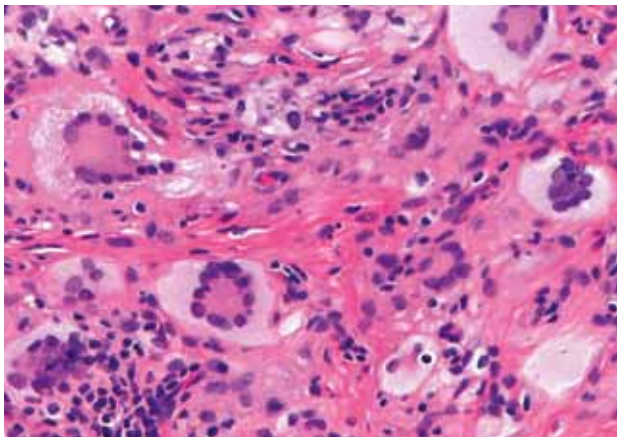

Fig2 - Histologic aspect. © B. Richert

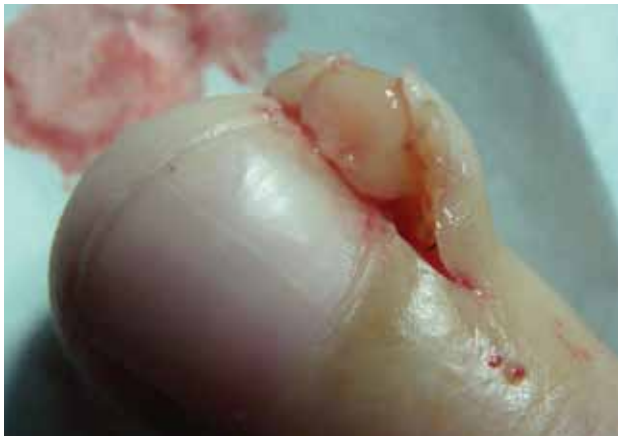

Fig3 - Per operative aspect. Incision of the lateral fold allows enucleation of the lesion. © B. Richert

A 58-year-old lady presented to our department for a painless skin colored nodule on the lateral nail fold **(Fig 1)**. She was a gardener, fond of roses, and was convinced that the lesion had started several months previously after she had pricked her finger with a thorn.
She had no remarkable medical history, did not suffer from any current disease and had not travelled outside Europe during the past year.
Palpation of the lesion revealed a nodule, mobile and not depressible on pressure. Ultrasound is shown on Fig 2 **(Fig 2)**.
Under local anesthesia the lateral nail fold was incised and the lesion very easily extirpated **(Fig 3)**.

What is your diagnosis?

Bertrand RICHERT

The giant cell tumour of the tendon sheath (GCTTS) is the second most frequent non-epithelial benign tumour of the hand and the fingers after the ganglion cyst. Despite its relatively frequent occurrence, it is rarely reported in the dermatological literature, perhaps because it is mainly dealt with by hand surgeons. Its pathogenesis remains unclear.[1, 2] A true neoplasm arising from either sesamoid bones, synovium or primitive mesenchymal cells has been proposed, but most authors favour the hypothesis that it may be a reactive inflammatory process. There is often a history of preceding trauma.[3] It occurs between 30 to 50 years of age and like myxoid cysts, is preponderant in females.[4] The tumour is primarily on the fingers, typically adjacent to the interphalangeal joints[5]: the index finger, thumb, and middle fingers in descending order of frequency, and shows no preference for either hand.[1, 6, 7] Involvement of the foot and toes is rare.[2] Although it is recognized as a condition that may involve the distal digit, there have been only 3 reports of periungual involvement.[3, 6, 8]

Typically, the tumour produces no symptoms and presents as a well-circumscribed, slow growing, lobulated firm mass with normal overlying skin at any point around an interphalangeal joint. Differential diagnosis of GCTTS includes myxoid cyst, epidermal cyst (as in our case), lipoma, fibroma, rheumatoid nodule, reticulohistiocytoma, sarcomas, and metastasis.[1-6] Granuloma annulare and erythema elevatum diutinum should also be considered.[9] Only 20% to 30% of GCTTS are diagnosed clinically before surgery.[1] The histology is characteristic. It consists of a mixed cell population of mononuclear cells with eosiophilic cytoplasm and vesicular nuclei, fibroblast-like cells, xanthomatous cells, siderophages, osteoclast-like cells and mononuclear inflammatory cells.[10] Although the condition is generally benign, malignant degeneration has been reported in exceptional cases.[11, 12] No spontaneous regression has been recorded and the treatment is surgery. The reported recurrence rate of 17% to 48% is probably due to the lobulated nature of the tumour, with occult extension around the tendon sheath. Failure to make the correct diagnosis and to dissect out the tumour to its full extent may increase the chance of relapse.

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The nail - What's new ? n° 6

Continuing Medical Education

Bruno FOUILLOUX, Elisa CINOTTI

Nail in confocal microscopy

Reflectance confocal microscopy (RCM) is an emerging technique which, with a real-time confocal microscope, uses reflected light to optically section living tissue at various depths, to examine and image layers of the skin, mucosa and the nail unit without stains or dyes in vivo, and recently also ex vivo.

RCM, developed and patented by Marvin Minsky in 1955, uses optical imaging to obtain high-resolution optical images with depth selectivity.[1] The key feature of RCM is its ability to acquire in-focus images from selected depths. In a confocal laser scanning microscope, a laser beam passes through a pinhole and then it is focused by an objective lens into a small focal volume of a specimen. Scattered and reflected laser light is then re-collected by the objective lens. After passing the pinhole, the light intensity is detected by a photodetection device, transforming the light signal into an electrical one that is recorded by a computer. Only the light reflected from the biologic structures at the selected plane is allowed to contribute to image formation. Since both the light and the microscope objective are focused on the same specific focal plane, objects and structures above and below the plane do not interfere with the formed image.[2]

RCM gives horizontal images of the analysed tissue with resolution at a cellular level and without alteration of the tissue surface. Skin and nails are ideal locations for exploration by RCM, because they are easily accessible sites. The depth to which the confocal microscope can optically penetrate is limited by the light penetration into the tissue and by the reflectivity of the observed structures and corresponds to 200-300 µm for skin tissue.

RCM distinguishes the different layers of the epidermis (stratum corneum, granulosum, and spinulosum) and the dermal epidermal junction and can image down to the papillary dermis.

Corcuff,[3] Leveque[4] and Piérard[6] were the first to use RCM to study the ultrastructure of the skin, whereas Kaufman and al.[2] showed that the unique properties of RCM make it possible to explore the capillary nailfold and the nails down to the deeper layers of the nail plate and nail bed.

Sattler et al.[6] have recently investigated healthy nail plates with RCM. The thickness of different layers, as well as structural details, were defined. RCM is able to display single corneocytes and the integrity of their borders. The nail plate can be scanned from the surface to the lower part adjacent to the underlying nail bed. Three different layers can be differentiated by RCM according to the intensity of the reflection. The superficial layer shows a brighter reflection, followed by a zone with a slightly poorer signal, followed again by a brighter zone in the deepest part.

Confocal microscopy in onychomycosis

Widely used methods to confirm a clinical diagnosis of onychomycosis often either yield negative results (e.g. direct miscroscopic examination) or are slow giving results (e.g. dermatophyte cultures). Hongcharu et al.[7] first reported the possible application of in vivo RCM for the diagnosis of onychomycosis. RCM produces high resolution images and has the great advantage of being non-invasive. Nails can therefore be imaged in their native state at high resolution and contrast without fixing, sectioning or staining. Hongcharu et al. correlated RCM findings with the results from routine KOH preparations. They hypothesized that RCM may be faster and more accurate in the diagnosis of onychomycosis,than the conventional microscope with KOH preparations

A 32 year-old Caucasian man had brownish discoloration of both big toenails. From the clinical findings, a diagnosis of onychomycosis was made. The authors performed both in vivo and in vitro confocal infrared microscopy from an affected nail. Full-thickness clippings of the affected nails were collected and imaged without any other preparation. Virtual sections were obtained in vivo by focusing the confocal microscope inside the nail plate.

In vivo confocal images from just below the surface of the nail revealed a network of branched hyphae **(Fig 4)**, and in vitro confocal images from the base of the nail also revealed branched hyphae. KOH preparations of the same specimens used in confocal imaging were also performed confirming the presence of the hyphae.

The treatment of onychomycosis usually requires systemic antifungal therapy. Since systemic treatments last several months and may cause serious adverse effects, isolation or identification of the fungi from the affected nails is necessary before starting the treatment. However, attempts to document fungal infection by KOH preparations and fungal culture are often inaccurate and unreliable. RCM is an additional tool that can be used in these cases.

In a prospective trial on 50 patients[8] RCM was compared to the gold standard techniques (culture, PAS-staining and PCR) as a tool to diagnose onychomycosis and showed a better sensitivity (79% vs 74%) and specificity (81% vs 76%) than KOH preparation.

In addition, RCM can also demonstrate the location and density of the fungi and is able to quantify the ”fungal load”.[9]

Bruno FOUILLOUX, Elisa CINOTTI

Confocal microscopy in melanonychia

The differential diagnosis of subungueal melanoma and nævus is often clinically challenging. In 2002 S. Ronger et al.[10] published the first large series of longitudinal melanonychia studied by dermoscopy which showed that dermoscopy could help in the differential diagnosis between benign and malignant causes of nail pigmentation. RCM has been shown to be useful in discriminating benign versus malignant melanocytic lesions of the skin, but it is not suitable to image the nail matrix in vivo, due to its limited penetration of 200-300 µm.

Management of melanonychia recommends a nail matrix biopsy in suspicious cases. If a malignant pigmentation (subungual melanoma) is confirmed by a histological examination, surgical treatment should be subsequently performed. The classical treatment of subungual melanoma consists of distal phalanx amputation. Nevertheless, many centres offer conservative treatment consisting of nail matrix and nail unit excisions. Sureda et al.[11] showed that conservative treatment provides better functional results and does not increase recurrence. However, surgical conservative treatment is still invasive and painful. A procedure to confirm a diagnosis of subungual melanoma intra-operatively could therefore be helpful.

At present, there is no accurate way to confirm a diagnosis of subungual melanoma intra-operatively. Histopathological examination of the nail matrix is not possible extemporaneously, because the size of the specimen is quite small and the diagnosis usually requires immunostaining. However, recent studies[12, 13] showed that the eponychium could be reclined during the nail biopsy procedure, in order to better visualize the nail matrix pigmentation and to perform intra-operative dermoscopy and RCM.

Hirata et al.[13] published a study about the intra-operative dermoscopic examination of the nail matrix and nail bed in cases of longitudinal melanonychia. They described four intra-operative dermoscopic patterns, which had better sensitivities and specificities for the aetiological diagnosis of longitudinal melanonychias than patterns observed by nail plate dermoscopy. However, some difficulties persist. For example, the so-called "regular brown line pattern", which was usually associated with a nævus in the series of Hirata, was also observed in two cases of early melanoma, illustrating the diagnostic difficulties between benign melanocytic hyperplasia and early melanoma. These diagnostic difficulties are well known in histopathology, and we cannot expect to get better specificity from dermoscopy, even if performed intra-operatively, than that obtained from histopathology.

Debarbieux et al.[12] evaluated the feasibility of intra-operative imaging of the nail matrix by both in vivo and ex vivo RCM and compared the obtained images with conventional histopathological sections. A biopsy was performed on the pigmented area of the matrix, after it had been exposed by reclination of the nail plate on nine patients seen for a suspicious melanonychia. RCM was performed in vivo on the pigmented area of the matrix before performing the biopsy and/or ex vivo on the fresh tissue. In most cases, the images obtained both by ex vivo and in vivo RCM were reliable enough to make the diagnosis and the slight loss of quality, sometimes observed in vivo because of subtle movements, did not have any impact on the diagnostic value of the observed features. Intra-operative RCM revealed sufficiently atypical cytological and architectural features to accurately suggest the correct final diagnosis of melanoma. A good correlation between RCM and histopathology was found: subungual melanoma was diagnosed intra-operatively in seven out of eight cases proved to be melanomas by histological examination **(Fig 5)**. The authors suggest that RCM is a promising tool for the intra-operative diagnosis of melanonychia, because it combines the advantages of dermoscopy (non invasive examination of the whole interesting area, without alteration of the epithelial surface) and histopathology (resolution at a cellular level). RCM offers a good contrast between melanocytes and adjacent structures. It permits the visualization of architectural and cytological features of melanocytic proliferation. Ex vivo examination can be used either alone, or as a complementary technique if the data provided by in vivo examination are not diagnostic.

In vivo RCM is particularly interesting for the diagnosis of nail disorders because it allows a fast and non-invasive examination, possibly reducing the number of biopsies in this sensitive anatomical site.

In vivo RCM examination is not sufficient and requires a biopsy. Ex-vivo RCM can assist surgery intra-operatively. Ex vivo RCM allows direct observation of cytological and architectural features of tissues at a resolution similar to classical histology, without needing fixation, freezing or cutting. Therefore, it can be a good tool for rapid diagnosis in nail pathology. Our experience of ex vivo RCM examination of nail biopsies and surgical samples convinced us that this technique is suitable for the nail apparatus and might be potentially useful for extemporaneous examination of surgical samples to ensure that margins are in sano (micrographic surgery). In our experience, images obtained by ex vivo RCM are of very good quality and correlate well with histological features. Moreover, examination can be performed on both sides of the nail tablet allowing examination of the deepest structures with a higher resolution than in vivo RCM.

However, to date, only a few aspects of nail disorders have been studied with RCM and more studies are needed to describe the RCM features of nail disorders.

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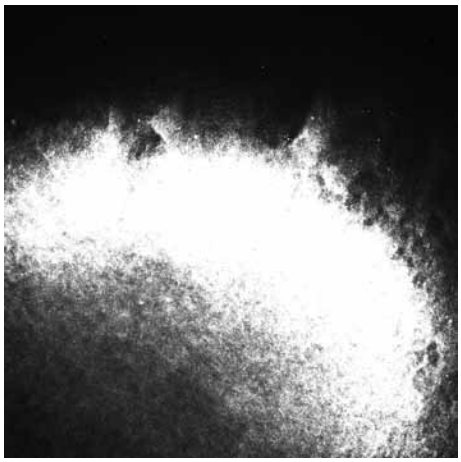

Fig1 - Brighter reflection of superficial layer. © E Cinotti

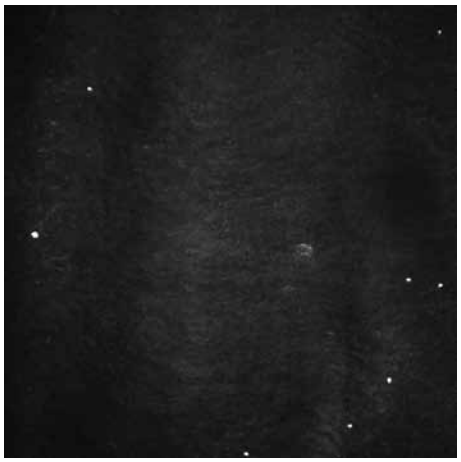

Fig2 - Poor signal in middle zone. © E Cinotti

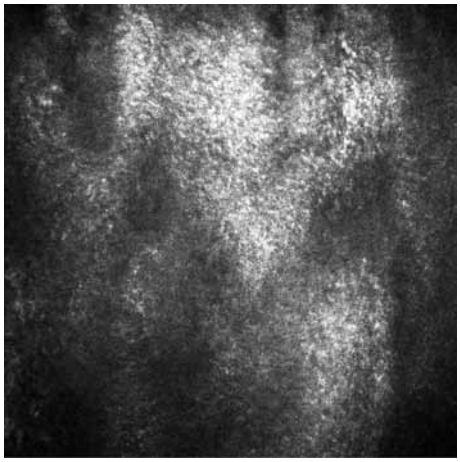

Fig3 - Brighter reflection in the deep zone. © E Cinotti

Fig4 - Network of branched hyphae in onychomycosis. © J.L. Perrot

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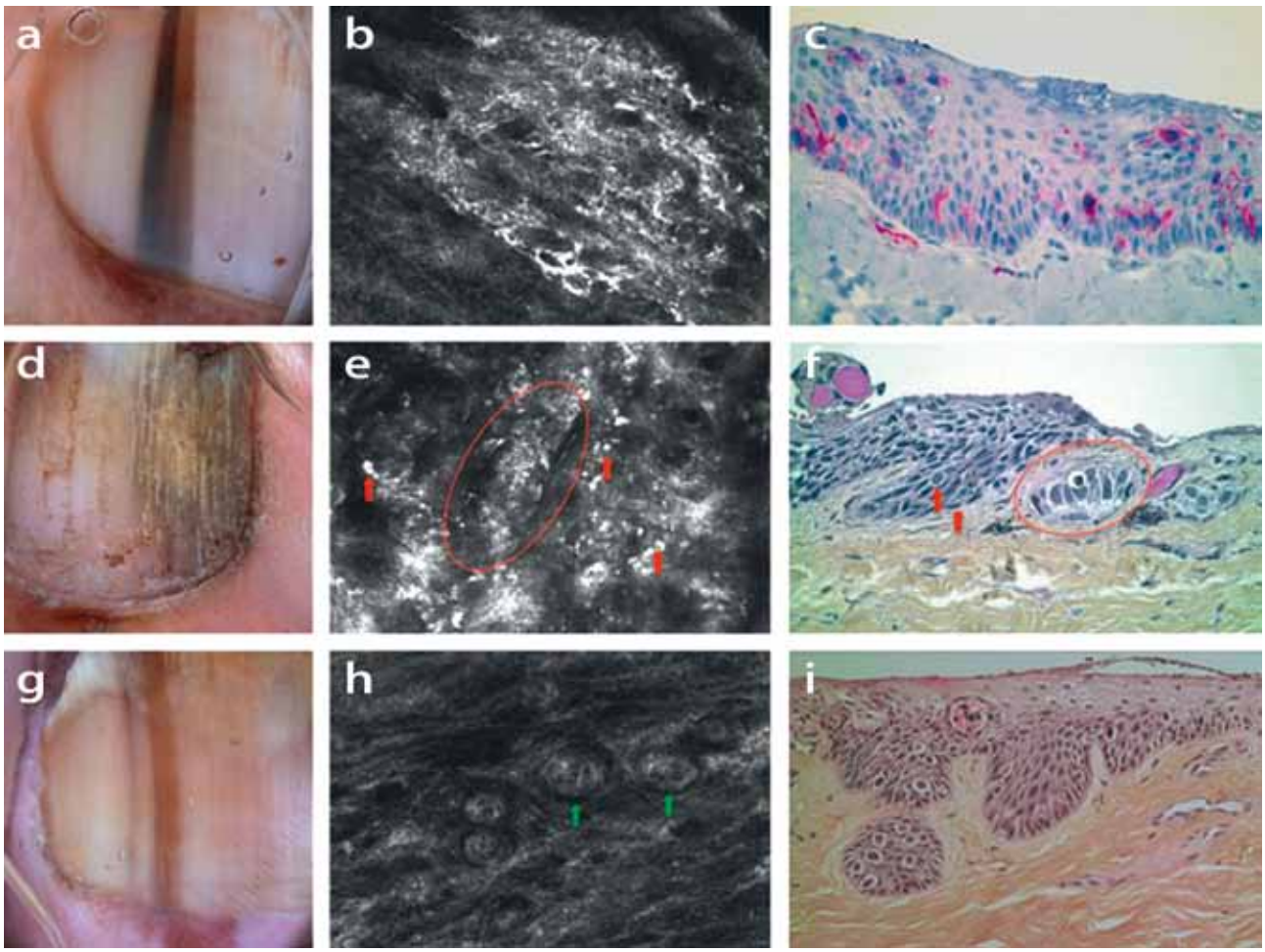

Fig5 - © S. Debarbieux

Patient 1 (a)
Dermoscopy of the nail plate showing Hutchinson sign, irregularity and triangular shape of the pigmentation. (b) In vivo reflectance confocal microscopy (RCM) examination showing melanocytic proliferation at the dermoepithelial junction. (c) Histopathological MelanA-stained section confirming an early melanoma. (d-f)

Patient 2 (d)
Dermoscopy of the nail plate showing a nonspecific pattern but the presence of a Hutchinson sign (slight pigmentation of the hyponychium, not seen on the photograph). (e) In vivo RCM examination showing isolated (red arrows) and nested (red circle) atypical large nucleated round bright cells. (f) Haematoxylin and eosin stained histopathological sections showing a malignant proliferation of isolated (red arrows) and nested (red circle) atypical melanocytes. (g-i)

Patient 3 (g)
Dermoscopy of the nail plate showing the irregularity of thickness and pigmentation of lines, a Hutchinson sign and a slight pigmentation of the hyponychium. (h) RCM ex vivo examination showing nests of moderately refractile atypical large nucleated cells in the papillary dermis (green arrows). (i) Histopathological correlation: interpapillary epithelial projections colonized by atypical melanocytes.

The nail - What's new ? n°6

notes

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