The revolutionalization of the treatment of onychomycosis

DIAGNOSTICS WITH OPTICAL COHERENCE TOMOGRAPHY (OCT) AND THERAPY BY MEANS OF PINPOINTE-FOOTLASER AS WELL AS ANTIMYCOTIC CREAM

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INTRODUCTION

Onychomycosis, the fungal infestation of the nails is a widespread health problem in the western industrial nations. With increasing prevalence it is increasingly affecting populations from countries with high temperatures when the lifestyle habits become similar to those in the industrial countries. In total more than 10% of the German population suffers from foot (athlete's foot) and/or nail fungus, with the incidence increasing at an older age. Specific gender differences have as yet not been described, however men appear to be somewhat more frequently affected by nail fungus. Immune deficiencies, also with patients with Diabetes mellitus, after chemotherapy, or with circulation disorders can strongly promote a nail fungus infestation. Further triggering factors are pronounced mechanical taxation of the feet with sportsmen/sportswomen or with orthopaedic problems. The risk factors for fungal infestation are here the continued wearing of closed shoes through the macerating influence of the sweat and the continuous shoe pressure, and the repeated affliction with micro traumas, haematomas and partial onycholysis of the foot nails. The nesting, growth and progression of an infestation of the nail organ with dermatophytes are then typical.
Due to the increased life expectancy a further increase in the prevalence of nail fungus infections is to be anticipated over the next years, as well as through the increase in contamination at sports facilities, bathing facilities, mass showering facilities, hotels and incubation in enclosed shoes.

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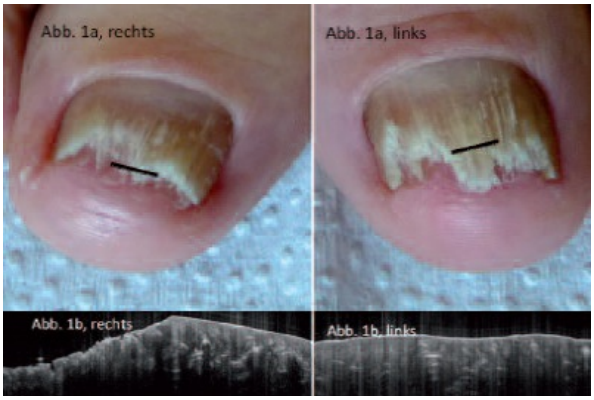

Fig. 1a, right **Fig. 1a, left**
Fig. 1b, right **Fig. 1b, left**

Fig. 1: 68-year-old patient with a long-term onychomycosis, as well as formation of crumbling nails.

a) Clinical photo of both large toes
b) In OCT clearly visible destruction, as well as complete infestation of the nail plate with fungus material, which in cross-section partially has the appearance of bar and partially arc structures.

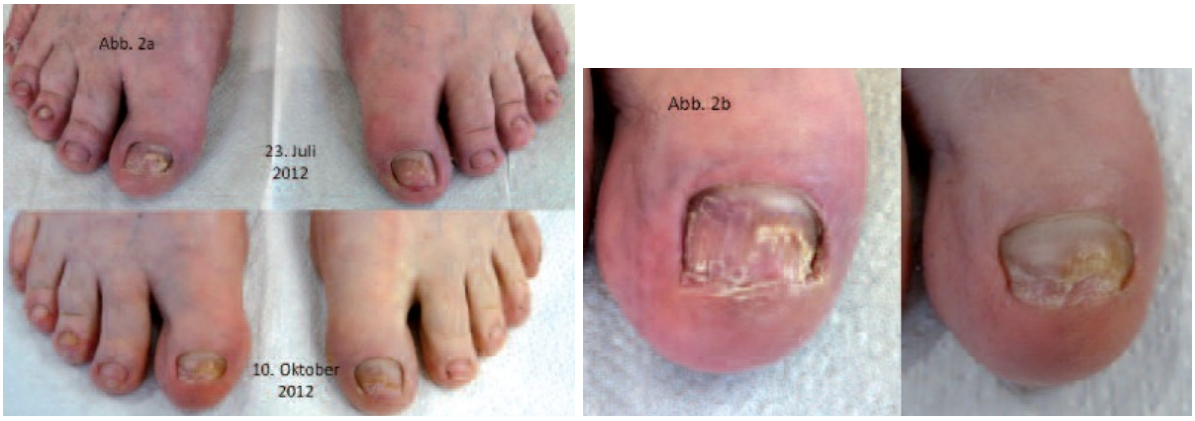

Fig. 2a:
July 23, 2012
October 10, 2012

Fig. 2a: Control of clinical progression with a 66-year-old patient after 3 months. One-time therapy with the Pinpointe-Footlaser and relapse prophylaxis with Terbinafin cream every second day.

Fig. 2b: Enlarged image of the right large toe nail before, as well as nearly 3 months after the Pinpointe-Footlaser therapy. Clearly visible restitution of the nail in the proximal portion.

DIAGNOSIS OF ONYCHOMYCOSIS

The diagnosis of onychomycosis is usually relatively easy, as the patients often come to the dermatological practice in an already relatively advanced stage with grey-white to yellowish discoloured and partially thickened or crumbly nail sections. Therefore, in most cases a visual diagnosis is possible. Nail changes such as striae cracks, whitish areas with beginning onycho-destruction not easily identifiable with the naked eye are far better assessed by means of dermatoscopy.
The substantiation of the fungus in culture was long required as validation for the infection, which due to the cultivation of the fungus, in practice often delayed the onset of the therapy. The microscopic diagnosis with K-OH, the dermato histopathological diagnosis with PAS staining or the polymerase chain reaction [7], which can substantiate fungal DNA with high specificity, are largely dependent on the sampling sites and often make a repeated visit to the physician necessary. With a negative result the physician will tend to call the patient in again to repeat the whole procedure.
Under the treatment and for control of the therapy success with onychomycosis the diagnosis on the nail is substantially more difficult. With application of topical preparations the preparation of a fungus culture is factually not a viable option, as during the scraping or cutting of the nail material the applied antimycotic can also prevent growth in the fungus culture.
More promising for success here is the diagnosis by means of microscopy of scraped or cut nail material, as well as the polymerase chain reaction (PCR). Both the latter mentioned methods are however relatively drawn out methods, and are associated with a large amount of work and are therefore nearly never used for control of the progression. They therefore do not permit any ad hoc decisions on the therapy. Microscopy and PCR are both ex vivo

diagnostic methods that do not allow further local allocation, and are above all not able to indicate the status, e.g. of all 10 toenails.
From today's perspective of the authors the previously mentioned disadvantages of the conventional diagnostic procedures for onychomycosis can be balanced and resolved through the application of a quickly performable imaging procedure, optical coherence tomography (OCT). Above all the acquisition of the baseline findings for comparison to the progression findings during the onychomycosis therapy can be quickly and safely accomplished during the visit of the patient.

OPTICAL COHERENCE TOMOGRAPHY IN THE DIAGNOSIS OF ONYCHOMYCOSIS

OCT diagnostics is already established in ophthalmologic diagnostics since many years [1], and is increasingly being used in dermatology for the diagnosis of skin tumours [2, 3].

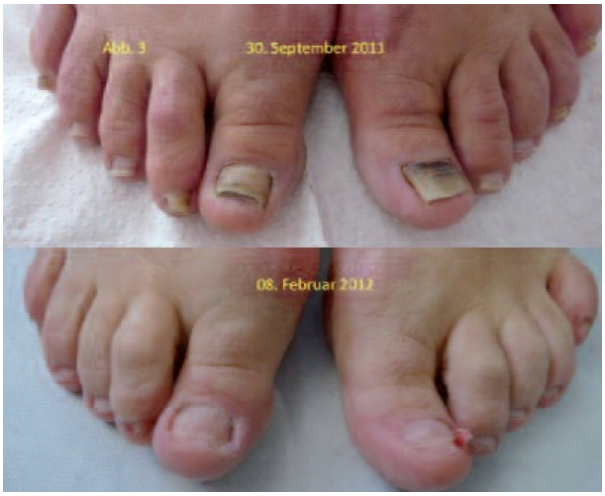

Fig. 3
September 30, 2011
August 21, 2012

Fig. 3: Clinical progression control with a 68-year-old female patient after PinPointe treatment combined with Terbinafin Cream. Improvement after 11 months.

TAB. 1: MEDICATION THERAPY OF ONYCHOMYCOSIS.

Topical
Bifonazol
Mikonazol
Ketoconazol
Ciclopiroxolamin
Amorolfine
Terbinafin

Systemic
Griseofulvin
Itraconazol
Fluconazol
Terbinafin

Depending on the used technique penetration depths of up to 2 mm with a resolution of up to 4 µm are possible. With OCT a concentrated infrared laser beam with a wavelength of 1300 nm is sent through the tissue, which is refracted and reflected through the structures in the tissue. A sensor in the device then comparatively measures the intensity of the reflected light. Due to the calculated refraction differences the device can then create black-and-white

section images and represent them in two dimensions (Vivosight, company Michelson Diagnostics, UK).
In the OCT with healthy subjects the transparent nail plate has a grey transparent appearance, whereas already the smallest amounts of enclosed fungal material appears hyper reflective and white due to the ventilation [4, 5]. As the images are already shown on a screen in real time, in vivo statements about the infestation and extent of the fungal overgrowth can be made. With the presented patient the central area of the toe nail plate D1 right and left is laced with dot, bar and arc shaped hyper reflective inclusions (white) (fig. 1). The OCT images are stored and are then easy to compare with the subsequent findings, for example to be able to take location specific decisions about the necessary therapeutic steps (fig. 4).
The examination by means of OCT is thereby completely pain-free, without side-effects and can be repeated any number of times.

THERAPY OF ONYCHOMYCOSIS WITH THE PINPOINTE LASER PROCEDURE

The start of the infestation of the toenails with the dermatophytes typically begins with a discrete discolouration of the distal ends of the toenails, respectively with loss of opacity of the paronychium, usually caused through the mechanical load situation on one of the large toes (Digitus 1), or also on the small toes (Digitus 5). The whitish streaks spread towards proximal and later leave a whitish surface area (distolateral subungual onychomycosis). Later the gap between the nail bed and nail plate thickens and imposes as subungual onychomycosis.
Further nails, initially on the same and then later on the other foot can be affected up to below the cuticle and up to the growth zone of the nail organ (stem cell region).
From the differential diagnosis perspective however, psoriasis of the nails [6], eczema nails and lichen should be considered. Hereditary onycho dystrophies should also be excluded.
In most cases the causative organisms are Trichophyton rubrum, in rarer cases also Trichophyton mentagrophytes, or Epidermophyton floccosum. It sometimes comes to a mixed infection with Candida albicans, or also with bacteria that can be associated with discolouration.
The most frequent affection pattern is the subungual infestation of the nail; here the causative organism is located below the nail plate deep in the nail bed. With advanced mycosis this makes it extremely difficult to eliminate the fungus with topical preparations, as the active substance is often not able to reach the source of the infection. Topical preparations can be recommended as special nail varnishes such as Amorolfine or Ciclopiroxolamin, or as solution (Ciclopiroxolamin), or as creams such as Terbinafine or others (Tab. 1).
Above all the toenails can in the normal state reach a thickness of approximately 1 mm. If it additionally comes to the development of unguis in turriculo or to onychogryposis, the nail thickness with subungual infestation is substantially larger and can reach the centimetre range. With massive subungual affection and penetration over the distal third of the nail plate the success of an effective topical therapy is not very promising.
This represents the indication for the oral therapy of the nail fungus with oral antimycotic agents such as Terbinafin, Itraconazol or also Fluconazol (Tab. 1). All the mentioned preparations have in common that with oral intake they lead to changes in the liver enzyme values, can trigger nausea and vomiting and are contraindicated during pregnancy and the breastfeeding period. With Terbinafin it can additionally also come to partially irreversible loss of taste and severe skin reactions.
With the same indications now a new and effective therapy option is available by means of thermolysis of the fungus material through coherent infrared light (1064 nm, 0.2 J per pulse) with a specially micro pulsed Nd:YAG laser (PinPointe^{TM}, Cynosure). This procedure is based on the pure thermal effect of heat cones - conducted through a very thin glass fibre cable and air (distance to the nail approximately 3 mm) – which can destroy the fungal nests in the nail and the surrounding tissue (in loco) and leave the perfused nail material untouched. The nail plate is then able to grow out healthy again. The PinPointe-Footlaser

was specially optimised to reach the affected areas with as high a fungus toxic energy dose as possible [8]. The painlessness and tolerability combined with effective therapeutic application was achieved through a small diameter of the glass fibre conductor (hand piece) and special micro-pulsing. The Pin-Pointe-Footlaser procedure was approved by the Food and Drug Administration (FDA) in USA in the year 2010 and has been officially authorised for marketing in Europe for the therapy of onychomycosis.
The therapeutic effectiveness is high, especially in combination with an accompanying topical antimycotic therapy for relapse prophylaxis. The authors have achieved very advantageous results with the PinPointe-Footlaser, if the patients have undertaken regular visits for control, if necessary after-treatment of individual areas with the PinPointe-Footlaser, and have continuously undertaken an external relapse prophylaxis by means of application of an antimycotic agent.

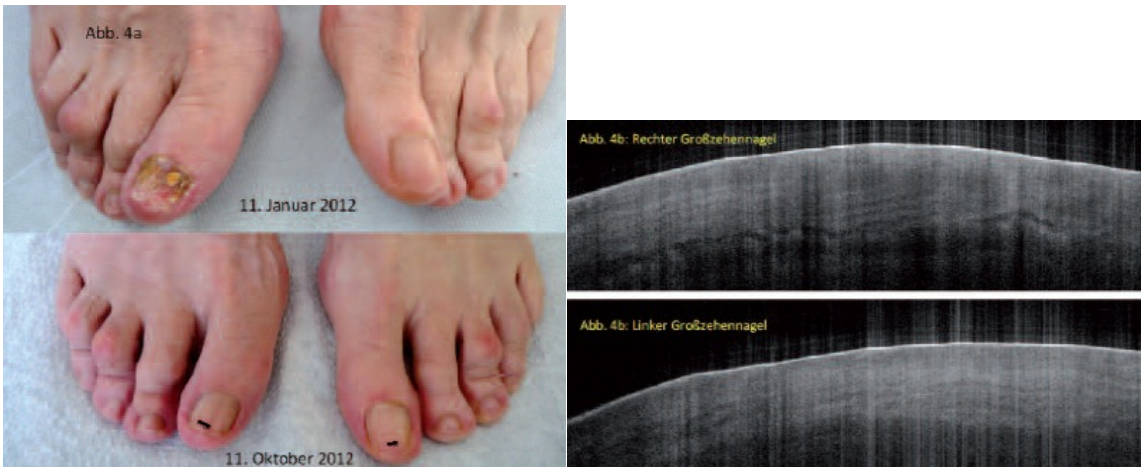

Fig. 4a
January 11, 2012
October 11, 2012

Fig. 4a: Clinical progression control (PinPointe-Footlaser and Terbinafin cream) after 9 months. Treatment of a 73-year-old female patient with completely affected large toe nail right. Control OCTs of the large toe (black bar).

Fig. 4b: Right large toe nail
Fig. 4b: Left large toe nail

Fig. 4b: Control OCTs of the distal nail plates. No fungal infestation is visible in the nail, nor in the nail bed. The surface of the nail plate is smooth and not cracked.

THE "MUNICH MODEL" OF THE PINPOINTE-FOOTLASER TRIPLE COMPONENT THERAPY

The PinPointe-Footlaser procedure is being used in Munich since the spring of 2010 and until now more than 300 patients have been successfully treated.
Initially the removal of superfluous, destroyed nail material under atraumatic conditions is important. The laser beam is often not able to penetrate up into the nail bed through the discoloured, dark, thickened nail material. A reduction of this material with atraumatic, mechanical technique before the laser treatment delivers good results (Tab. 2).
Subsequently the PinPointe-Footlaser therapy is performed as initial therapy. Prior to this the dermatoscopic examination of all 10 toenails ensures an optimised review of the overall infestation, a photographic documentation with the digital camera is started. The laser treatment of the affected nails usually comprises of two passes of point-shaped penetration

of the nail plate with the laser beam, with severest infestation 3-4 passes. The paronychium is traversed 3 to 4 times. During the first treatment – which usually includes all 10 toes –the nails are treated with 15,000 to 25,000 laser impulses (200 mJ/cm2), depending on the level of affection. A local anaesthetic is not necessary.
Thirdly, continuous relapse prophylaxis with Terbinafin or Ciclopiroxolamin cream at the edge of the nail, respectively at the paronychium, every 2. day, in the morning is provided for. This should initially be performed up until the next clinical check-up appointment after 2–4 months. Further return visits with photographic documentation are performed after 4–6 months, as required after 6–8 months and 10 to 12 months. The continuation of the relapse prophylaxis should be discussed and decided at the check-up appointments and be specifically continued with persisting fungus infestation.
To prevent formation of a subungual pomade crust with regular cream application on the nails, weekly cleaning with a nail brush at the edge of the nails is to be recommended. Thereby with the PinPointe-Footlaser procedure the laser therapy is not the sole effective therapeutic agent, but the combination of three treatment measures yields the prolonged therapeutic success (Tab. 2). Conversely however, without the application of the laser therapy a comparable therapy success is not able to be achieved solely with atraumatic nail removal and topical therapy. Through the laser treatment the proximal portion of the nail organ up to the stem cell area becomes re-established and it comes to healthy outgrowth of the fresh nail substance (fig. 2). With the depicted patient, two and a half months after the PinPointe-Footlaser treatment it has come to clearly apparent nail growth from proximal (fig. 2b). Over the progression it is very important to perform an external relapse prophylaxis. This prevents a repeated penetration and the spreading of the fungus mycelium over the nail bed and over the many open fissures of the previously damaged nail.
With a further female patient, apart of the external application of Terbinafin cream (every 2. day) the atraumatic removal of the distal, whitish nail material was regularly continued (fig. 3). In the most favourable case a recovery of the nail with this treatment protocol always requires the growth time of the nail plate from proximal to distal (fig. 4a). With the shown female patient a restitution of the nail plate of the right large toe was able to be observed over 9 months. To continue with the assessment of the therapeutic success an optical coherence tomography (OCT) was performed. The examination did not provide any indications for the presence of an onychomycosis (fig. 4b).
As a further example of an OCT examination for control of the progression of the PinPointe-Footlaser treatment a residual, distal infestation of the left large toenail is shown (fig. 5). With the represented cross-section images of the lateral paronychium of both large toes, merely a distal infestation of the nail bed left is visible (fig. 5, see right bottom).

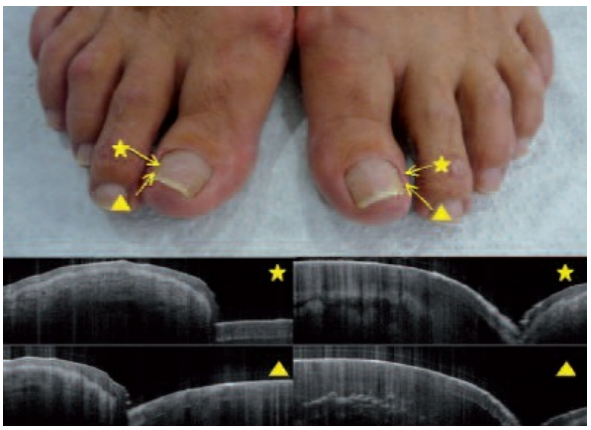

Fig. 5: Clinical control of the progression after therapy with Pinpointe-Footlaser and Terbinafin cream with a 62-year-old female patient. Visually and according to OCT there is merely a residual infestation of the left large toe nail distal. In the OCT the localisation of the fungus infestation in the nail bed is visible, the nail plate is free.

TAB. 2: TREATMENT OF ONYCHOMYCOSIS ACCORDING TO THE MUNICH MODEL OF THE PINPOINTE-FOOTLASER THREE-PART THERAPY.		
First step After diagnostic evaluation and photographic documentation	Atraumatic reduction /removal of destroyed nail material (crumbling nail)	Mechanical abrasion
Second step After dermatoscopy	Initial therapy with the PinPointe-Nd:YAG laser (1064 nm)	2–4 passes, depending on the severity of the infestation
Third step Protection	Continuous relapse prophylaxis with antimycotic cream at the nail edges and paronychium every second day	Terbinafin cream Ciclopiroxolamin cream
Additionally Prevention of pomade crusts	Weekly	Cleaning with a nail brush
Regular clinical checkups	photo documentation, dermatoscopy, OCT Targeted laser therapy	After 2–4, 4–6, 6–8 and 9–12 months

CONCLUSIONS

A completely new approach to the therapy of severe onychomycosis was established in 2008 in USA. By means of a micro pulsed infrared laser a certain procedure was able to be developed that passes through nails with fungal infestations and can thereby deactivate the existing fungus structures up to the nail bed without damaging the nail organ. Undesirable side-effects did not occur in the more than 300 treated patients described in this work. The difficult task of preventing reinfection of the previously damaged nail required an optimisation of the sole PinPointe-Footlaser therapy. Over the past two and a half years it has been possible to establish a very successful therapy regime consisting of a triple component therapy with reduction of the damaged nail tissue, laser treatment and consistent external therapy with antimycotic cream (Tab. 2). Also the very extensive, complete deep foot nail mycosis infestations were able to be fundamentally restored. This means that with severe onychomycosis a systemic therapy with tablet intake has been able to be replaced. Further advantages of the PinPointe-Footlaser therapy, apart from the fast efficiency are freedom from side effects, no necessity for control of the blood values and a lower frequency of visits to the physician compared to the administration of systemic antimycotic agents. In addition the compliance of the patients suffering from chronic nail fungus, partially with decades of previous frustrated therapy attempts, is very good. The Munich model of the PinPointe-Footlaser therapy as triple factor therapy is accepted by nearly all patients and is performed consistently. Also beyond the healing of the nail a continuation of the external relapse prophylaxis with antimycotic cream is advised, for example after swimming, fitness or sports activities.

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