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Fusarium onychomycoses in Switzerland – a mycological and histopathological study

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Summary

Objectives: Onychomycoses in temperate climates are most commonly due to dermatophytes, particularly *Trichophyton rubrum*. Non-dermatophyte nail infections are much less frequent, and their diagnosis requires a careful and repeated search for a potential dermatophyte that may have been overgrown in culture.

Materials/Patients/Methods: A series of histological slides of suspected onychomycoses with uncommon fungal morphology prompted us to search for non-dermatophytic molds causing dermatophytosis-like nail infections.

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Results and Conclusions: Thirty cases were identified by culture as *F solani*, *F oxysporum, F dimerum* or *F* spp, and two more were only diagnosed histopathologically. None of these patients was immunocompromised. Treatment was mostly unsuccessful with terbinafine whereas itraconazole showed a moderately better treatment result; in all cases, a topical ciclopirox nail varnish in a hydroxychitosan base was added.
The study demonstrates that *Fusarium* species are important nail pathogens also in Central Europe.

Key words: Onychomycosis – Fusarium species – Culture – Histopathology – Treatment

Introduction

Onychomycoses (OM) are worldwide occurring fungal infections of the nail apparatus. Most cases are distal or distal-lateral subungual OM and due to dermatophytes [1]. Yeasts and other non-dermatophytic molds are rare and not generally accepted as nail pathogens; however, some *Candida* species have acid proteases capable of digesting keratin, and some molds, including *Fusarium* spp are undoubtedly able to invade nails and subungual keratin [2]. English (1979) stated that molds should only be accepted as nail pathogens when the same species is grown three times in culture and without simultaneous growth of a dermatophyte [3]. These stringent criteria are rarely fulfilled in clinical routine although they might be useful for the choice of an antifungal drug, particularly in recalcitrant cases [4].

Fusarium species are common plant pathogens and occur both in tropical as well as temperate and even arctic climates [5]. They cause important crop damages and are the source of mycotoxins also in Central Europe including Switzerland [6]. Of the more than 300 known phylogenetically different species, most opportunistic *Fusarium* pathogens belong to the *F solani* complex, *F oxsporum* complex and *F fujikoroi* complex. In tropical countries, *Fusarium* spp cause keratitis and onychomycoses. They are also feared causes of systemic infections in severely immunocompromised individuals, particularly under chemotherapy and in acute leukemias [7]. Onychomycoses in immunocompetent persons due to *Fusarium* spp in Europe are mainly reported from southern countries

such as the Balkans, Italy, France and Spain and mostly occur in toes that often have been traumatized before [8, 9]. They appear to be more frequent in women than in men [10, 11].

During our routine examinations of onychomycosis-suspicious nails using direct microscopy, culture and histopathology, we encountered a number of cases with an uncommon fungal morphology (Figure 1) prompting us to search for the cause.

Material and methods

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article related to micro-organisms.

The culture results of nail specimens from 2010 till 2016 were searched from the files of the Mycology laboratory, Institute for Infectious Diseases, Univ Berne and compared with the results of the histological examinations. As direct microscopy of KOH cleared specimens was noncontributory and usually did not give a hint at a particular *Fusarium* etiology, the presence of fungal elements was noted but not included into the final analysis. Cultures were grown on Sabouraud agar with gentamycin and chloramphenicol, Czapek's agar, mycosel agar and the micromorphology was evaluated using lacto fuchsin stain. Histological sections were prepared from nail clippings with as much subungual keratin as possible, stained with hematoxylin and eosin (H&E) and PAS and viewed at 100, 200 and 400x magnifications. In case of doubt, Grocott silver stain was performed.

Results

The institutional files revealed 28 cases of *Fusarium* spp, of which 15 were *F solani*, 5 were *F oxysporum,* 7 were *F* species, and 1 was *F dimerum* (Figure 2). Two more cases were seen in Freiburg, Germany, and another two in Porto, Portugal (EH[3,4]); of these four, two were mycologically diagnosed as *F* species and 2 were only diagnosed histopathologically.

Histopathology of the clipped nail and subungual keratosis demonstrated fungal elements in the deep nail plate layer and the underlying keratosis. Leukocyte accumulations as seen in Munro's microabscesses were common and surrounded by parakeratosis. PAS exhibited fungal filaments with very variable diameter and often

ampullar dilatations. The hyphae showed marked segmentation with frequently very short segments (Figure 1). Nine-teen of the specimens demonstrated basophilic fungal cell walls and thus allowed the diagnosis of fungal infection also in H&E sections (Figure 1a).

Discussion

Fusarium species are new emergent nail pathogens now observed almost worldwide. Originally known as plant pathogens in warm climate zones with an important potential to harm crops and as a source of fungal mycotoxins in cereals they were observed as causes of *Fusarium* keratitis in rural areas mainly, but not exclusively, of tropical countries and as occasional pathogens of onychomycoses in tropical and subtropical regions. *Fusarium* nail infections are rarely diagnosed in Central Europe and difficult to treat. Clinically, they cannot be distinguished from the common dermatophyte onychomycoses, but histologically they show slender to relatively thick septate hyphae often with characteristic ampullar dilatations in their course. In culture, they form whitish cottony colonies with a brownish reverse side. Lactophenol cotton blue stain reveals characteristic banana shaped macroconidia in addition to microconidia and hyphae.

Nondermatophyte molds cause about 10% of the onychomycoses with a range from 1.45% to 17.6% [12]. *Fusarium* spp alone were estimated at 1 to 6% of onychomycoses [13], but were found in a higher percentage in other studies [14, 15, 16]. The differences in prevalence may account to various geographical regions and climate zones and certainly also to techniques of examination [17]. It is evident that *Fusarium* onychomycoses go unnoticed in most cases and are often simply dismissed as another case of therapy-resistant onychomycosis or as mold contamination. The percentage of *Fusarium* spp as nail pathogens varies from 9 – 44% of mold infections [18]. Women are more frequently affected and fingernails are apparently also involved in tropical countries [16]. All types of onychomycoses may be due to *Fusarium* spp [9, 19] including onychomycoses with associated paronychia [20] and melanonychia [21]. Whether diabetes mellitus is a risk factor is not yet entirely clear [22].

Fusarium onychomycoses are important as they may be the source of life-threatening infections in immunocompromised individuals and cause deep seated fusarioses in burns, large ulcers and foreign body granulomas [23, 24]. Patients with these infections should not work in the food industry, kitchens and hospitals, particularly newborn and cancer wards as well as surgical theaters.

Treatment of *Fusarium* infections is difficult. Fluconazole is usually inactive and also terbinafine often only gives a modest response. Itraconazole is more active [25], and both voriconazole and high-dose amphotericine are currently the drugs of choice [26, 27]. Natamycin was found to be very active against *F fujikuroi* [28]. One case was reportedly cured with 2 sessions of Nd-YAG laser [29] whereas another study showed no cure with laser treatment [30].

In summary, *Fusarium* species are emergent pathogens also in Central Europe. They should be searched for in case of mold growth in culture and an uncommon morphology in histopathology of the nail. Their identification is important as they are more difficult to treat and may have particular hygienic implications for a variety of professions and contact with premature babies, immunosuppressed individuals, and cancer patients.

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Legends

Figure 1. Onychomycosis due to *Fusarium solani*. Both the hematoxylin & eosin (H&E) (1a) as well as the PAS stain (1b) show fungal filaments of variable diameter with some ampullar dilatations. Usually, H&E does not stain fungi, particularly not dermatophytes, The fungi invade the deep nail plate layer as well as the parakeratosis surrounding a Munro-abscess like accumulation of neutrophils. Original magnification x400.

Figure 2. Distribution of culturally identified *Fusarium* species.