

Non-dermatophytic onychomycosis. An underestimated entity? A study of 51 cases

Nicht-Dermatophyten-Onychomykose: Eine unterschätzte Krankheit? Eine Studie von 51 Fällen

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Schlüsselwörter. Onychomykose, Schimmelpilze, antimykotische Chemotherapie, Itraconazol, Terbinafin.

Summary. The aim of our study was to evaluate the incidence, the clinic characteristics, the therapeutic antifungal response and the evaluation of side-effects in 51 non-dermatophytic onychomycosis cases which were observed in a case-study of 1012 patients, affected by different types of onychopathy, attending the Mycology Ambulatory of San Paolo Hospital, Milan, Italy during the period 1994–97.

Zusammenfassung. Ziel der Studie war, Inzidenz, klinische Charakteristika, Therapieerfolg und Nebenwirkungen bei 51 Fällen von Nicht-Dermatophyten-Onychomykose zu bewerten, ausgelesen aus einer Fallstudie mit 1012 Onychopathie-Patienten der mykologischen Ambulanz des San Paolo-Hospitals in Milano, Italien, im Zeitraum 1994 bis 1997.

Introduction

Onychomycosis is one of the most frequent causes of onychopathy. In Australia, UK and USA the incidence of onychomycosis has been estimated at about 3% of the total population, increasing to 5% in older people [1, 2]. The number of patients affected by onychomycosis is continually growing and every year the number of micro-organisms recognized as capable of parasitizing the ungual

lamina directly is growing all over the world [3]. In the last few years, non-dermatophytic onychomycosis, once thought to be non-existent or considered very rare is instead rapidly increasing, particularly in Europe, where it is currently responsible for onychomycosis with percentages varying from 1.6 to 6% according to different studies [4]. Among the responsible aetiological agents, species belonging to the genera *Scopulariopsis*, *Aspergillus*, *Fusarium* and *Acremonium* should be mentioned. It has also been demonstrated that many other non-dermatophytic moulds that are usually considered laboratory contaminants or environmental saprophytes, can parasitize the ungual lamina directly [5, 6]. These include some species of genera *Alternaria*, *Curvularia*, *Penicillium*, *Scytalidium*, *Hendersonula*. Other filamentous non-dermatophytic fungi can exceptionally cause onychomycosis too. Recently, as a consequence of the increase in the number of cases of immunodepression all over the world, more attention has been given to this wide, but generally not pathogenic, group of fungi and this has led to the identification of a greater number of effective or potential aetiological agents of onychomycosis.

Patients and methods

Between January 1994 and January 1997, 1012 patients with different forms of nail disorders were examined in the Mycology Ambulatory of San Paolo Hospital, Milan. The mycological diagnosis was established by microscopic examination in 40% KOH of the ungual fragments and cultural examination incubated for 2 weeks at 27 °C on

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Table 1. Distribution of cultural positives

		Feet	Hands	Total	Percentage
Dermatophytes	<i>T. rubrum</i>	246	44	290	49
	<i>T. mentagrophytes</i> var. <i>interd.</i>	102	11	13	19
Yeasts	<i>Candida</i> sp.	3	132	135	24
	<i>Scopulariopsis brevicaulis</i>	18	0	18	3.06
	<i>Aspergillus niger</i>	8	0	8	1.36
Moulds non-dermatophytic	<i>Aspergillus</i> sp. (<i>fumigatus</i> , <i>flavus</i> , <i>terreus</i>)	6	0	6	1.02
	<i>Fusarium oxysporum</i>	8	6	14	2.38
	<i>Acremonium</i> sp.	3	0	3	0.51
	<i>Alternaria alternata</i>	0	1	1	0.17
	<i>Curvularia</i> sp.	1	0	1	0.17
	Total positives	395	194	589	

Sabouraud glucose agar with and without chloramphenicol. The confirmation of the pathogenetic significance of the non-dermatophytic onychomycosis agent was carried out with two repetitions of the culture every time the first culture showed the growth of a mould. This enabled us to exclude from the case-study all occurrences of possible contamination. Microscopic preparation with Lugol solution from the colonies of the non-dermatophytic moulds was used for mycological identification.

The patients affected by non-dermatophytic onychomycosis (51 cases) were treated orally for 3 months with one of two possible therapeutic schemes: 30 patients were treated with terbinafine (250 mg daily) and 21 patients with itraconazole (200 mg daily). All of the patients affected by non-dermatophytic onychomycosis were otherwise healthy and not immunodepressed. During the 3 months of treatment, clinical and microscopic examinations were conducted monthly together with the recording of possible side-effects. In all patients mycological culture was performed at the end of therapy. At a follow-up examination, 6 months after the therapy, the patients were assessed to determine whether they were completely cured or still affected by onychomycosis.

Results

In 589 cases (395 involving toe nails and 194 involving finger nails) the aetiologic agent of onychomycosis was established after repeated cultural examinations. (Table 1) We found that dermatophytes were the more responsible aetiologic agents of onychomycosis, resulting in a total of 403 patients (68%). The toe-nails were more affected. In contrast, the yeasts of the genus *Candida* (24%) were found to be more pathogenic as regarding the finger nails, mainly in middle and older aged women. Non-dermatophytic onychomycosis were 8% of all ungual infections (Table 2).

If a mould was isolated after the first cultural examination, its aetiologic significance for a non-dermatophytic onychomycosis was confirmed after the third positive cultural examination, whereas all other cases were considered to be just contaminants. The non-dermatophytic onychomycosis included infections due to *Scopulariopsis brevicaulis*, *Fusarium oxysporum*, *Acremonium* sp., *Aspergillus* sp., *Alternaria alternata* and *Curvularia* sp. The infections were mostly localized to the toe nails. The finger nails were involved particularly if the patients did gardening work or were employed in agriculture, as this can be a cause of contamination due to handling soil or plants, which are places where the opportunistic fungi are more widely present.

In our study, *Scopulariopsis brevicaulis* was shown to be the cause for ungual mycosis in 18 patients out of 589 (3.1%). In five of 17 cases an association with infection due to *Trichophyton rubrum* was noted. Among the moulds *S. brevicaulis* is the agent most frequently responsible for onychomycosis, and represented 35% of total non-dermatophytic onychomycosis in our study (Table 3). In all our cases a distal subungual onychomycosis of the biggest toe nail was observed, bilaterally in four cases. In contrast to the data reported in the literature, seven patients were aged under 50 years and four of them were under 30 years of age. No contemporaneous cutaneous infection with *Scopulariopsis brevicaulis* was discovered in any of our patients. We also observed three cases of onychomycosis

Table 2. Distribution of onychomycosis in aetiologic groups

Fungal groups	<i>n</i>	%
Dermatophytes	403	68
Yeasts	135	23
Moulds	51	9
Total	589	100

Table 3. Incidence of non-dermatophytic moulds

Fungal species	n	%
<i>Scopulariopsis brevicaulis</i>	18	35
<i>Fusarium oxysporum</i>	14	27
<i>Aspergillus niger</i>	8	16
Other <i>Aspergillus</i> sp.	6	12
<i>Acremonium</i> sp.	3	6
<i>Alternaria alternata</i>	1	2
<i>Curvularia</i> sp.	1	2
Total	51	100

due to *Acremonium* sp., equal to 0.5% of total or to 6% if we consider only non-dermatophytic onychomycosis (Table 3). All our patients were of Caucasian race and, when questioned, they did not mention any journey to tropical or subtropical regions, where these fungi are more prevalent. The corresponding clinical pictures were two cases of white superficial onychomycosis (of which one was bilateral) and one case of distal subungual onychomycosis.

The ungual infections due to *Fusarium oxysporum* were 2.4% of all onychomycosis investigated and 27% if only non-dermatophytic onychomycosis is considered (Table 3). The preferential localization was the big toe nail (eight cases) with a white superficial onychomycosis associated with paronychia, but we also found six cases of infections localized in the finger nails, four of which had an unusual aspect. In 12 cases of 14 a different degree of paronychia was present.

The infections by *Aspergillus* sp. represented 2.4% of all onychomycosis (of which *Aspergillus niger* alone was 1.4%) and 28% if only non-dermatophytic onychomycosis are considered (of which *Aspergillus niger* is 16% alone) (Table 3). In all cases the distal subungual onychomycosis was localized in the toe nails, especially the big toe nail. When questioned, it was found that the patients used to go bare-footed in the garden.

Finally, we observed one case of finger nail onychomycosis by *Alternaria alternata* and one case of toe nail by *Curvularia* sp.

The patients affected by non-dermatophytic onychomycosis were treated for 3 months, using one of two therapeutic schemes consisting of terbinafine (250 mg daily) or itraconazole (200 mg daily). Thirty cases (15 *Scopulariopsis brevicaulis*, eight *Aspergillus* sp., five *Fusarium oxysporum*, two *Acremonium* sp.) were treated with terbinafine (250 mg daily), and the other 21 cases (three *Scopulariopsis brevicaulis*, six *Aspergillus* sp., nine *Fusarium oxysporum*, one *Acremonium* sp., one *Alternaria alternata*, one *Curvularia* sp.) were treated with itraconazole (200 mg daily). We observed

complete clinical healing and negative results of mycological examinations after the therapy in 48 cases of 51. In two cases of *Fusarium* infections localized in the big toe nail, both treatment schemes were followed by the patients with a 6-month interval between them, but they were not effective and the patients remain affected by onychomycosis. In one of these two cases we saw a moderate cellular defect of neutrophilic chemotaxis. In five other cases we began with one therapeutic scheme, but because of the occurrence of some side-effects, after some time we successfully administered the other scheme. In particular, in four cases we had to stop treatment with itraconazole because of increased blood pressure, important lower-limb oedemas and diuresis reduction; in another case we stopped giving terbinafine because of a widespread cutaneous rash. In three other cases treated with itraconazole side-effects such as vomiting, lower-limb oedemas and headache occurred only at the end of the third month of treatment, allowing the completion of the therapeutic cycle. In the case of onychomycosis caused by *Curvularia* sp. we do not know the course of the therapy because the patient did not come back to us after the first month of treatment.

Discussion

The ability of non-dermatophytic moulds, in particular *Alternaria* sp., *Scopulariopsis brevicaulis* and *Aspergillus niger*, to attack the ungual fragments has been already been demonstrated in 1965 by English and afterwards by Roobaert [7, 8]. However, it is only in the last few years that the number of cases of non-dermatophytic onychomycosis has greatly increased, mainly in Europe, associated with cases of immunodepression and in immunocompetent subjects.

The incidence of non-dermatophytic moulds in the pathogenesis of onychomycosis is variable in the epidemiologic studies so far conducted, with regard to the methodologies used and to the migratory phenomenon of populations within individual countries; this is particularly evident for European cases (from 1.5 to 6% of all onychomycosis) [1, 2]. Our case-study shows major evidence of onychomycosis caused by non-dermatophytic moulds (8%), which may be due to the high percentage of farmers or people whose hobby is gardening who came to our clinic. In consequence of the migratory flows, fungi of genus *Scytalidium*, which can exceptionally cause onychomycosis in our country, but more frequently in west African countries and in Thailand, have now become frequent causes of onychomycosis also in

the UK and Australia [3, 9]. Other factors which have contributed to the spreading of non-dermatophytic onychomycosis are immunodepressed patients and the immigration phenomena [10–13]. Recently, some authors have suggested that an untreated non-dermatophytic onychomycosis could be a dangerous portal of entry for deep-seated and disseminated mycoses, that are hard to treat in immunocompromised subjects [14–18]. Therefore, correct diagnosis and rapid treatment of non-dermatophytic onychomycosis immunodeficiencies is indispensable.

Onychomycosis caused by moulds in immunocompetent patients, as were all our cases, particularly affect people who handle soil and plants because such fungi usually live in the soil as parasites or epiphytes on many plants [19–22]. Experience in the treatment of non-dermatophytic onychomycoses is still limited due to the broad variety of aetiological agents, some of which are endowed with intrinsic resistance properties, e.g. *Fusarium* species. Generally a longer treatment period must be considered [23–36]. In our case-study we adopted two possible therapeutic schemes for 3 months: either 250 mg terbinafine per day or 200 mg itraconazole per day. On the basis of our experience, both therapeutic schemes can be considered effective in the treatment of non-dermatophytic onychomycosis in immunocompetent patients.

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