FACTORS AND CLINICAL FEATURES ASSOCIATED WITH FAILURE TO ACHIEVE A CLINICAL CURE AMONG ONYCHOMYCOSIS PATIENTS WITH MYCOLOGICAL CURE

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Abstract. Treatment of onychomycosis may not always result in a return to normal nail appearance. We retrospectively reviewed the medical records of patients treated for toenail onychomycosis that achieved mycological cure at Siriraj Hospital, Bangkok, Thailand from January 2010 to May 2020 to determine the clinical cure rate and factors associated with failure to achieve a clinical cure. Mycological cure was confirmed by a negative potassium hydroxide (KOH) preparation and negative fungal culture. A clinical cure was defined as at least an 80% improvement in the nail plate without clinical evidence of onychomycosis. Treatment outcomes were assessed by evaluation of toenail photographs by two dermatologists. Demographic data, selected risk factors, oral antifungal treatment types and physical examination of patients with and without clinical cure were recorded and compared. Sixty-seven subjects were included in the study. The mean (±standard deviation (SD)) age of the total study subjects was 65 (±12) years; 54% male. Thirty-eight subjects (57%) had a clinical cure 12 months after initiating treatment. The mean (±SD) age of subjects who failed to have a clinical cure (70 ± 11 years) was significantly (p = 0.011) older than the mean age of subjects who had a clinical cure (62 ± 12 years). Subjects who were significantly less likely to have a clincal cure were those with peripheral vascular disease (p = 0.003), having onychophosis (p = 0.004), having onychauxis (p = 0.004) and having a pincer nail (p = 0.022). In summary, a large proportion of our study subjects failed to have a clinical cure and the factors significantly associated with this were older age, having peripheral vascular disease, onychophosis, onychauxis and pincer nail. We conclude that subjects with these associated factors should be warned prior to treatment that even though they may have mycological cure, they may not have a clinical cure.

Keywords: dermatophyte, onychomycosis, mycological cure, clinical cure, toenail onychomycosis

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INTRODUCTION

Onychomycosis of the toenails is a common fungal infection. Dermatophytes are the main causative organism and can be effectively treated with systemic antifungal medication (Kreijkamp-Kaspers *et al*, 2017). After treatment is completed, a mycological cure is confirmed by a negative potassium hydroxide (KOH) preparation and negative fungal culture (Scher *et al*, 2007). A clinical cure is defined as at least an 80% improvement in the nail plate without clinical evidence of onychomycosis (Scher *et al*, 2007; Salakshna *et al*, 2018).

Onychomycosis may reduce patient quality of life (Gupta and Mays, 2018). Despite mycological cure, residual nail abnormalities persist in many patients. Patients often expect to have a normal toenail following onychomycosis treatment but this may not occur if they have other concomitant conditions affecting nail appearance or post-onychomycosis treatment onychodystrophy from severe fungal nail infection. Concomitant nail disorders may be under-diagnosed prior to having onychomycosis treatment (Zaias *et al*, 2014). Some nail disorders, such as traumatic onychodystrophy, are not easy to distinguish from onychomycosis. Mycological laboratory testing is needed to discriminate between onychomycosis and traumatic onychodystrophy.

We aimed to determine the rate of clinical cure in patients with mycologically cured onychomycosis and the factors associated with failure to achieve a clinical cure in order to predict prognosis after treatment.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients diagnosed with toenail onychomycosis who received treatment and achieved mycological cure at the Outpatient Nail Clinic, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand during January 2010-May 2020. We located these records by searching for patients with the ICD-10 diagnostic code B35.1. Patients aged >18 years with a positive potassium hydroxide (KOH) preparation slide of a nail scraping and a fungal culture showing dermatophyte growth were included. Patients with a follow-up time of <12 months, charts with incomplete data, fungal cultures showing a mixed fungal infection

and those with a history of having a preexisting nail disorder were excluded. Extracted data included demographic data, underlying diseases, immunosuppressive drug usage, foot hyperhidrosis, relationship with agriculture, bare-foot walking, having a history of a pedicure or pet exposure, results of the KOH preparation slide, fungal culture results, treatment regimen, outcomes, and pre- and post-treatment 2-view photographs of the infected nails. All dorsal and hyponychial (frontal) nail photographs were independently reviewed by two investigators. Cases where investigators had discordant conclusions were discussed until there was agreement. Lesions were categorized as having nail plate changes or periungual tissue changes. Nail plate changes consisted of onychauxis, abnormal nail plate curvature (pincer nail), and frictional melanonychia. Periungual tissue changes consisted of onychophosis, onychocryptosis, hypertrophy of the lateral lip, onycholysis and toe-tip callus formation. Foot deformities, such as hallux valgus, hallux rigidus, adjacent second toe impingement and plantar calluses were recorded. Treatment outcomes were assessed after 12 months. Patients with mycological cure, defined as having a negative microscopic examination and negative fungal culture after treatment. A clinical cure was defined as having at least an 80% improvement in the nail plate without clinical evidence of onychomycosis. Patients with mycological cure were then classified according to whether or not they had achieved a clinical cure. The proportions of patients with and without a clinical cure were recorded and factors associated with failure to achieve a clincal cure were analyzed.

Statistical analysis

Statistical analysis was performed using PASW Statistics for Windows (version 18.0; SPSS Inc, Chicago, IL). Descriptive analyses used for our evaluation consisted of proportions, means, medians, maximums and minimums. The Chi-square and Fisher's exact tests were used to compare differences in demographic data by group. The generalized estimation equation was used to compare differences in proportions, crude odds ratios (cOR), and 95% confidence intervals (95% CI) for specific nail findings. A p-value <0.05 was considered statistically significant.

The study was approved by the Siriraj Institutional Review Board (COA no. Si 468/2018).

RESULTS

A total of 67 subjects were included in the study; 54% male. The mean (±standard deviation(SD)) age of study subjects was 65 (±12) years. Thirty-eight subjects (57%) had a clincal cure 12 months after initiation of treatment. The mean (±SD) age of subjects who failed to have clinical cure (70 ± 11 years) was significantly

(p = 0.011) greater than the mean (±SD) age of subjects who had a clinical cure (62 ± 12 years) (Table 1). The number of subjects with peripheral vascular disease who had a clinical cure (8%) was significantly (p = 0.003) lower than the number of subjects without vascular disease who had a clinical cure (38%).

The most common types of onychomycosis observed among study

Table 1

Association with onychomycosis outcomes among study subjects for slected demographic and treatment factors (N = 67)

Characteristics	No clinical cure (N = 29)	Clinical cure (N = 38)	p-value
Male sex, *n* (%)	18 (62)	18 (47)	0.232
Mean ± SD age in years	70 ± 11	62 ± 12	0.011
Factors potentially associated with onychomycosis*, *n* (%)			
Agriculture occupation	6 (21)	13 (34)	0.224
Foot hyperhidrosis	10 (34)	8 (21)	0.219
Had a pedicure	1 (3)	3 (8)	0.628
Walking barefoot	2 (7)	5 (13)	0.690
Pet exposure	6 (21)	12 (32)	0.319
Immunosuppression	4 (14)	7 (18)	0.745
Peripheral vascular disease	11 (38)	3 (8)	0.003
Diabetes	6 (21)	4 (11)	0.309
Treatment of anychomycosis, *n* (%)			
Terbinafine	16 (55)	15 (39)	0.202
Fluconazole	10 (35)	16 (42)	0.526
Itraconazole	1 (3)	6 (16)	0.129
Topical treatment	2 (7)	1 (3)	0.574

SD: standard deviation

*One person could have more than one factor

subjects in our study were distal and lateral subungual onychomycosis (97%); the big toenail was the most frequently affected (73%). Subjects without clinical cure were significantly more likely (crude odds ratio (cOR): 4.92; 95% confidence interval (CI): 1.66-14.55; $p = 0.004$) to have onychauxis (nail plate thickness) (Fig 1), pincer nail (cOR: 5.33; 95% CI: 1.26-22.47; $p = 0.022$) (Fig 2) and onychophosis (cOR: 6.06; 95% CI: 1.76-20.86; $p = 0.004$) that subjects with clinical cure (Fig 3) (Table 2). None of the observed foot abnormalities among study subjects in our study (plantar callus, hallux valgus, toe impingement) were significantly associated with the failure to have a clinical cure.

The most common dermatophytes identified on nail fungal culture were: *Trichophyton mentagrophytes* (55%), *T. rubrum* (40%) and *T. tonsurans* (3%). The most common antifungal agents used to treat study subjects were terbinafine (31 cases; 46%), fluconazole (26 cases; 39%), and itraconazole (7 cases; 10%). Three patients received only topical antifungal treatment.

DISCUSSION

In our study, 43% of subjects did not have a clinical cure. Older age and of peripheral vascular disease were associated with a significantly lower chance of having clinical cure. This may be because older patients and patients with peripheral vascular disease tended to have more severe cases of leading to traumatic or ischemic nail bed damage and onychodystrophy.

Concomitant traumatic nail dystrophy may be the main reason why patients did not have normal nail appearance after onychomycosis treatment. Onychophosis, pincer nail, and onychauxis, which are the signs of traumatic nail dystrophy, were significantly associated with a failure to have a clinical cure in our study subjects. Most studies have reported that clinical cure is less common than mycological cure (Gupta *et al*, 2020), which was seen in our study. This might be explained by inadequate follow-up periods, variable criteria for clinical cure, subjective assessments and the presence of concomitant nail disorders, including traumatic nail dystrophy. We found that traumatic nail dystrophy is associated with the failure to achieve a clinical cure in the mycologically-cured onychomycosis patients. Nail plate changes from the hyponychial view (such as onychauxis and pincer) and changes in surrounding tissue (onychophosis) were also significantly associated with failure to have a clinical cure in our study subjects. However, nail plate changes seen from the dorsal view (such as leukonychia and onycholysis) were not significantly associated with failure to have a clinical cure in our patients and usually resolved after onychomycosis treatment. This highlights the importance of examining the nails in both the hyponychial and dorsal views is very helpful to guide diagnosis and

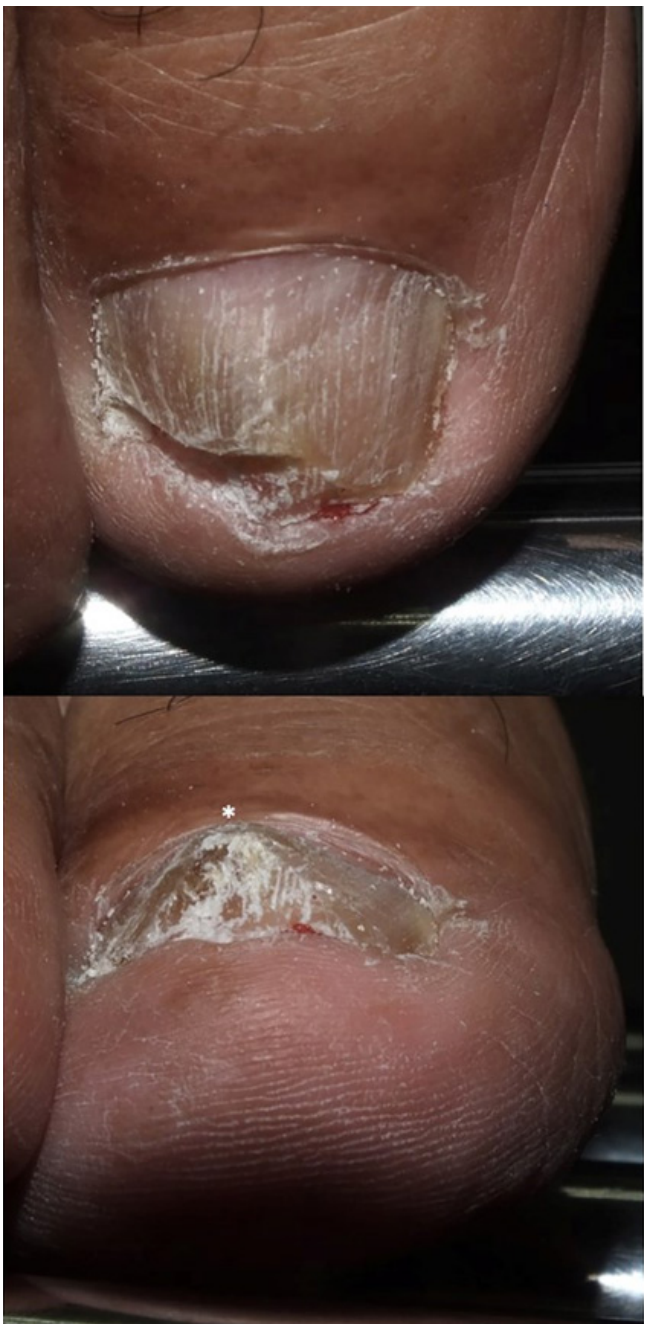

Fig 1 - Onychauxis (*) from dorsal and hyponychium views

Fig 2 - A pincer nail (*) from dorsal and hyponychium views

Fig 3 - Onychophosis (*) from dorsal and hyponychium views

Table 2

Association between selected foot, toe and nail characteristics and onychomycosis treatments outcomes among study subjects (N = 67)

Characteristics	No clinical cure (N = 29)	Clinical cure (N = 38)	Crude Odds ratio	95% confidence interval	*p*-value
Nail signs*, *n* (%)					
Dorsal view					
Nail plate discoloration	14 (48)	25 (66)	0.99	0.99 - 1.00	0.356
Dermatophytoma	4 (14)	3 (8)	1.75	0.35 - 8.67	0.489
Melanonychia	7 (24)	8 (21)	1.00	0.99 - 1.00	0.674
Onycholysis	8 (28)	12 (32)	1.00	0.99 - 1.00	0.654
Hyponychial view					
Damaged appearance	15 (52)	15 (39)	1.00	0.99 - 1.00	0.459
Onychauxis	19 (66)	8 (21)	4.92	1.66 - 14.55	0.004
Pincer	11 (38)	3 (8)	5.33	1.26 - 22.47	0.022
Tissue surrounding signs*, *n* (%)					
Dorsal view					
Onychophosis	19 (66)	6 (16)	6.06	1.76 - 20.86	0.004
Hyponychial view					
Toetip callus	14 (48)	6 (16)	1.00	0.99 – 1.00	0.202
Onychocryptosis	5 (17)	2 (5)	1.00	0.99 - 1.00	0.409

Table 2 (cont)

Characteristics	No clinical cure (N = 29)	Clinical cure (N = 38)	Crude Odds ratio	95% confidence interval	*p*-value
Foot deformity signs*, *n* (%)					
Hallux valgus	9 (31)	15 (39)	0.81	0.25 - 2.54	0.719
Toe impingement	5 (17)	7 (18)	1.00	0.99 – 1.00	0.768
Plantar callus	13 (45)	16 (42)	0.94	0.33 - 2.68	0.912
Pathogens, *n* (%)					
Trichophyton mentagrophytes	19 (66)	18 (47)	1.00	0.99 – 1.00	0.376
Trichophyton rubrum	8 (28)	19 (50)	1.00	0.99 - 1.00	0.334
Trichophyton tonsurans	1 (3)	1 (3)	1.24	0.07 - 20.83	0.881
Microsporum gypseum	1 (3)	0	N/A	N/A	0.433

N/A: not applicable/available

*One person could have more than one factor

perhaps prognosis.

Onychauxis consists of thickened nails. Increased nail thickness can be found in many conditions, such as aging, ichthyosis, Darier's disease, psoriasis and repeated trauma (Baran *et al*, 2003; Cohen and Scher, 1992). Increased nail thickness has been associated with poor outcomes in onychomycosis treatment (Sigurgeirsson, 2010). Pincer nail is characterized by an increase in the transverse curvature along the longitudinal axis of the nail that may also be caused by mechanical force (Lee *et al*, 2011). We found that onychauxis and pincer nails are associated with treatment outcomes in patients with onychomycosis.

Repeated minor trauma can result in tissue hyperplasia. Onychophosis is the term applied to callus formation in lateral nail fold caused by pressure from adjacent toes, tight shoes or a pincer nail (Baran *et al*, 2003). These signs are frequently found in patients with hallux valgus foot deformity. A toetip callus is another example of hyperkeratotic changes that can occur in a hammer, a clawed toe or with tight footwear (Baran *et al*, 2003). This sign is also characteristic of asymmetric gait nail unit syndrome (Zaias *et al*, 2014). These two signs are suggestive of repetitive trauma that can lead to traumatic nail dystrophy. Prolonged trauma may result in permanent nail changes that do not normalize after onychomycosis treatment. In our subjects, the risk for failure to achieve a clinical cure is six times greater when onychophosis is present.

Our study had limitations. First, patients with missing data or mixed fungal infections were excluded from the study. Second, there are no widely accepted definitions for traumatic nail signs. We tried to address this problem by using consensus from two investigators. Third, the 12-month follow-up period may be insufficient. About 12 months is often needed for an entirely new nail to grow out but toenails may not fully regrow for up to 78 weeks (Shemer *et al*, 2013). Finally, data on abnormal foot dynamics, footwear and abnormal foot deformities were not available.

In conclusion, among out study subjects with mycological cure only 57% achieved a clinical cure. Older age, peripheral vascular disease, onychophosis, onychauxis, and pincer nails were significantly associated with the failure to achieve a clinical cure. To our knowledge, ours is the first study to provide data on traumatic nail signs in terms of prognosis after the treatment of dermatophyte toenail onychomycosis. Patients with traumatic nail signs before treatment were less likely to experience a clinical cure. A thorough examination for traumatic toenail signs from the hyponychial and dorsal view is important. Physicians should advise patients with dermatophyte toenail-onychomycosis, especially those with these factors, that the normalization of the nail after treatment may be difficult and prolonged.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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