Clinical Characteristics and Mycology of Onychomycosis in Autoimmune Patients

WARANYA BOONCHAI, MD*,
CHANAI MAUNGPRASAT, BEd*,
KANOKVALAI KULTHANAN, MD*,
PUAN SUTHIPINITTHAM, MD*

Abstract

Onychomycosis is the most common nail disorder in adults. Predisposing factors are immunosuppression, poor peripheral circulation, diabetes mellitus, increasing age, nail trauma, and tinea pedis. Autoimmune patients, who carry many of these predisposing factors, have never been studied. Autoimmune patients, with underlying autoimmune skin diseases; pemphigus, systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, dermatomyositis and cutaneous vasculitis, as well as having abnormal-appearing nail(s) with suspicion of fungal nail infection were included. Clinical information was obtained. The causative organisms were identified by potassium hydroxide preparation and cultured. Duration of onychomycosis in autoimmune patients was twice longer than in non-autoimmune patients. Of those with mycological proven onychomycosis, the autoimmune patients had significantly more affected nails ($p < 0.05$; χ^2, two-sided) compared to the non-autoimmune patients but there was no difference in the affected fingernails or toenails and clinical type of onychomycosis. *Candida* spp was the most frequently found in autoimmune subjects compared to dermatophytes, *Trichophyton rubrum*. However, dermatophytes especially *Trichophyton rubrum* was the most common causative organism in non-autoimmune samples, followed by *Candida* spp. The causative organisms were more frequently discovered in autoimmune patients, whether by potassium hydroxide (KOH) or culture, than in non-autoimmune patients ($p < 0.05$; χ^2, two-sided).

Key word : Onychomycosis, Tinea Ungium, Autoimmune Diseases

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MAUNGPRASAT C, SUTHIPINITTHAM P
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* Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Onychomycosis is the most common nail disorder in adults, responsible for up to 50 per cent of all nail diseases[1]. The prevalence of onychomycosis differs across the world due to socio-economic and cultural factors[2]. Overall prevalence of onychomycosis was approximately 3-7 per cent[3-5], but somewhat higher in certain groups of patients such as diabetic patients[6]. Predisposing factors were immunosuppression[7,8], poor peripheral circulation[9], diabetes mellitus[6], increasing age[7], trauma, and tinea pedis[5,7].

A variety of fungal organisms can cause onychomycosis, including dermatophytes, yeasts and non-dermatophytic moulds. Dermatophytes are the most common pathogens for onychomycosis. Yeasts can not only be observed as saprophytes but can also cause onychomycosis, accounting for 1-2 per cent [1]; *C. albicans* and other *Candida* spp, especially in immunosuppressive patients[2]. Non-dermatophytic moulds are found to cause onychomycosis in a limited number of cases with *Fusarium* spp and are particularly dangerous in immunocompromised patients[10].

In the past, epidemiological studies concerning onychomycosis were performed in special population groups such as school children, subjects visiting swimming baths[10], subjects with specific occupations[11,12] or patients with underlying diseases like diabetes[6,13]. Autoimmune patients seem to carry many predisposing factors such as immunosuppression, poor peripheral circulation but somehow they have never been studied. This study aimed to study the clinical characteristics and mycological data of onychomycosis in these high-risk autoimmune patients.

MATERIAL AND METHOD

This is a prospective, observational and transversal study, conducted in the routine outpatient autoimmune clinic, in the Department of Dermatology of Siriraj University Hospital. All autoimmune patients having abnormal-appearing nail(s) and suspicion of fungal nail infection, without topical or systemic antifungal in the previous month, were included. There was no patient selection for sex and age. The following information was obtained: age, gender, underlying autoimmune skin disease, immunosuppressive medication, and duration of the present clinically abnormal nail(s). The clinical characters of the nail(s) were examined and classified by dermatologists. According to Baran et al[14], onychomycosis was classified into 5 clinical types: 1) distal-lateral subungual onychomycosis (DLSO), 2) white superficial onychomycosis (WSO), 3) proximal subungual onychomycosis (PSO), 4) endonyx onychomycosis and 5) total dystrophic onychomycosis. The authors were concerned that prolonged exposure to water might be one of the predisposing factors to onychomycosis, so information was obtained about the occupational environment of the patients and classified it as 'wet' or 'dry' exposure. While 'wet' means patients exposed to water most of the time e.g. housewives, chef and 'dry' means patients exposed to water only in their daily routine life including business people, salesmen, students.

The mycological examination consisted of identification of the fungus in the standard potassium hydroxide preparation and culture growth of the fungus in a suitable medium. The nail specimens were cultured in both cycloheximide and non-cycloheximide containing Sabouraud-dextrose media. If pure growth of dermatophytes was identified, it was simply considered as a causative pathogen. In the case of growth of yeast or non-dermatophyte mould, its impact as a causative agent was considered by using the following criteria. As stated for confirmation, the mould must be present where no dermatophytes were found, five cultures out of 20 must be positive and non-dermatophyte mycelia should be found under the microscope[15,16].

Results were evaluated by descriptive statistics and in the case of nominal variables were assessed by using the two-tailed χ^2 test.

RESULTS

The demographic data of the studied population is shown in Table 1. There were 19 patients with underlying autoimmune skin diseases containing 4 pemphigus, 10 SLE, 2 MCTD and one each of scleroderma, dermatomyositis and cutaneous vasculitis. The other group consisted of 29 patients without underlying autoimmune skin diseases. There was no statistical significance in age, or environmental exposure to water (Table 1). The number of females in the autoimmune group was 4 times higher than those in the non-autoimmune patients. The duration of onychomycosis in the autoimmune patients was twice as long as the non-autoimmune patients.

Of the patients with mycologically proven onychomycosis (Table 2), the autoimmune patients had significantly more affected nails compared to

Table 1. Demographic data.

	Autoimmune patients (19 cases)	Non-autoimmune patients (29 cases)
Male : female ratio	1 : 8.5	1 : 2.2
Age (mean ± SD, yr)	40.5 ± 9.8	44.8 ± 14.7
Exposure to a moist environment *	1 : 2	1 : 1
Duration of onychomycosis (mean ± SD, yr)	2.2 ± 2.8	1.1 ± 1.5

* $p > 0.05$ (χ^2, 2-sided)

Table 2. Characteristics of mycologically proven onychomycosis.

	Autoimmune patients	Non-autoimmune patients
Number of nail(s) affected*:		
Single : multiple	1 : 1.7	1 : 0.4
Site of nail(s) affected$^{\pi}$:		
Finger: toe	1.3 : 1	2.5 : 1
OM type (%)$^{\pi}$:		
DLSO	73.7	65.5
PSO	10.5	13.8
SWO	5.3	0
TD	5.3	20.7

* $p = 0.015$ (χ^2, 2-sided)
$^{\pi}$ $p > 0.05$ (χ^2, 2-sided)

Table 3. Recovery of fungi from infected nails.

Isolated fungus	Autoimmune patients (%)	Non-autoimmune patients (%)
Dermatophytes	21	38
T. rubrum	100	64
T. mentagrophyte	-	27
M. canis	-	9
Yeast	26	24
Candida spp		
Non-dermatophyte moulds	16	21
Fusarium spp	33	50
Aspergillus niger	-	17
Hendersonula	-	33
Cladosporium	33	-
Curvularia	33	-
KOH-positive, no fungus grown	-	10
KOH-negative, no fungus grown	37	7

the non-autoimmune patients who mostly had only a single affected nail, $p < 0.05$ (χ^2, two-sided). However, there was no difference in the affected nails, fingernails or toenails, and clinical types of onychomycosis between the two groups, $p > 0.05$ (χ^2, two-sided). If positive microscopy was taken as the sole criteria, the frequency of onychomycosis of clinically abnormal-appearing nail(s) would be 63 per cent and 93 per cent in the autoimmune group and non-autoimmune group, respectively (Table 3). Whereas, the

frequency would be 83 per cent of the non-autoimmune subjects if the positive culture was required as the criteria.

Of the organisms identified from the non-autoimmune samples, dermatophytes were the most commonly isolated fungi (38%). On the contrary, *Candida* spp was the most frequently found in the autoimmune subjects (26%). Of the dermatophytes, *Trichophyton rubrum* was still the most common isolate in both groups. The causative organism was more frequently discovered in the non-autoimmune patients, whether by KOH or culture, than in the autoimmune patients, $p < 0.05$ (χ^2, two-sided). However, spectrum of the causal fungi was seldom different between the two groups (Table 3). Of the KOH-positive specimens, cultures from the specimens of patients with underlying autoimmune disorders grew more than those from underlying non-autoimmune disorders. However, clinically abnormal-appearing nails without documented fungi were observed more often in autoimmune patients (37%).

DISCUSSION

This is a primary study of onychomycosis in a special patient population focusing on autoimmune patients. Surprisingly, autoimmune patients carry various predisposing factors, immunosuppression, poor peripheral circulation, but have never been studied. To the authors' knowledge, the present study is the first of its kind. Females were predominant in the group of autoimmune patients possibly due to the nature of the autoimmune disease itself. However, sex-dependency has never been proved as a risk factor for onychomycosis[5]. The age, mean and SD, in both groups in the present study were comparable. Exposure to moist circumstances seems not to play a role in the occurrence of onychomycosis.

The duration of onychomycosis in the autoimmune patients was twice as long as in the non-autoimmune patients. This indicates the delay in diagnosis possibly due to 1) ignorance of the doctor and patients to abnormal-appearing nail(s) or 2) misinterpretation of abnormal-appearing nail(s) as belonging to the autoimmune disease. There were significantly more multiple nails affected in the autoimmune group compared to the others. The finding reveals more extensive involvement in the autoimmune group possibly due to delay in diagnosis, slower nail growth or perhaps rapid progression of the organism. A history of concomitant intake of immunosuppressive agents for their autoimmune disorder (e.g. systemic steroid, cyclophosphamide or azathioprine) is also an important point apart from immune deregulation of the underlying autoimmune disease. However, the authors could not draw a definite conclusion from the present study because of the small sample size.

Onychomycosis of the fingernails was more common than toenails in both groups, which was different from Western reports[1]. This may due to the difference in life style as with the climate in Thailand, people tend to wear more breathable shoes. Clinical characteristics of onychomycosis showed insignificant difference between both groups ($p > 0.05$, χ^2 two-sided).

A variety of fungal organisms can cause onychomycosis, including dermatophytes, yeast and non-dermatophytes moulds. The most common isolated organism is yeast (26%); *Candida albicans* in patients with underlying autoimmune disorders. However, dermatophytes (38%), especially *Trichophyton rubrum*, was still found more frequently in non-autoimmune patients and also in autoimmune patients. Generally, dermatophytes are the most common pathogens for onychomycosis, with *Trichophyton rubrum* as the most frequently isolated organism[1,2,5,17,18]. Yeast can also cause onychomycosis, accounting for 2-14 per cent[1,17,18], however, the authors found this to be somewhat more common than previous reports. *Candida albicans* were the most commonly found among yeast[17-19], the same as in the present study. Non-dermatophytic moulds can produce onychomycosis in about 8-14 per cent of cases[1,16]. Tosti et al[16] considered mould onychomycosis was a sign of immunodeficiency. For instance, *Fusarium* onychomycosis was believed to be a very serious disease in immunocompromised patients[20,21]. From the present study, mould onychomycosis was not significantly associated with systemic diseases and isolated *Fusarium* spp played a trivial role in the patients with underlying autoimmune disorders.

The causative organism was rarely discovered from clinically abnormal-appearing nails in autoimmune patients, whether by KOH or culture, than in non-autoimmune patients, $p < 0.05$ (χ^2, two-sided). This may indicate that nail abnormalities in patients with underlying autoimmune disorders can occur and lead to misdiagnose as onychomycosis more often than in normal hosts. Of the KOH-positive specimens, the cultures from the patients with underlying autoimmune disorders were grown more often than those without underlying autoimmune disorders. The data suggest that the specimens from patients with underly-

ing autoimmune disorders carried more viable fungi as a result of the immunosuppression state of the patients.

In conclusion, onychomycosis in patients with underlying autoimmune disorders may be misinterpreted and left untreated resulting in involvement of multiple nails. Therefore, physicians should take a more active approach to nail condition in this group of patients. There was no clue in the clinical characteristics, however, the causative fungi are more likely to be *Candida* spp than dermatophytes. The present study may encourage all practitioners to look for fungal nail infection in abnormal-appearing nail(s) in this risk group of patients.

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ลักษณะทางคลินิกและชนิดของเชื้อราของโรคติดเชื้อราที่เล็บในผู้ป่วยออโตอิมมูน

วรัญญา บุญชัย, พบ, กนกวลัย กุลทนันทน์, พบ*,*
ไฉน เหมือนประสาท, กศบ, ป่วน สุทธิพินิจธรรม, พบ**

การติดเชื้อราเป็นโรคที่พบบ่อยที่สุดในกลุ่มโรคของเล็บ โดยมีปัจจัยส่งเสริมการติดเชื้อได้แก่ ภาวะภูมิคุ้มกันต่ำ เบาหวาน ผู้สูงอายุ ระบบการไหลเวียนเลือดบกพร่อง เล็บเสีย หรือผู้ที่เป็นกลากที่เท้า ในกลุ่มผู้ป่วยออโตอิมมูนที่มีปัจจัยเสี่ยงต่าง ๆ เหล่านี้กลับไม่เคยได้รับการศึกษาถึงอุบัติการณ์ ลักษณะทางคลินิกและชนิดของเชื้อรามาก่อน การศึกษาในครั้งนี้เป็นการศึกษาในกลุ่มผู้ป่วยออโตอิมมูนที่มารับการรักษาในคลินิกผิวหนัง โรงพยาบาลศิริราชและตรวจพบความผิดปกติของเล็บ ผลการศึกษาพบว่าในกลุ่มผู้ป่วยออโตอิมมูนมีระยะเวลาของการเป็นโรคมานานกว่าผู้ป่วยอื่นสองเท่า และมักมีการติดเชื้อราพร้อมกันครั้งละหลายเล็บ ($p < 0.05$; χ^2, two-sided) เชื้อราก่อโรคที่พบบ่อยสุดได้แก่ *Candida* spp และรองลงมาเป็นกลุ่ม dermatophyte ซึ่งเป็น *Trichophyton* rubrum 100% ในขณะที่ผู้ป่วยกลุ่มควบคุม เชื้อราต้นเหตุเป็น dermatophyte เชื้อ *Trichophyton rubrum* มากกว่า *Candida* spp

คำสำคัญ : โรคเชื้อราที่เล็บ, กลาก, ออโตอิมมูน

วรัญญา บุญชัย, กนกวลัย กุลทนันทน์,
ไฉน เหมือนประสาท, ป่วน สุทธิพินิจธรรม
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* ภาควิชาตจวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700