Onychomycosis in patients with chronic leg ulcer and toenail abnormalities*

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Abstract: Nails have a limited number of reactive patterns to disease. Accordingly, toenail changes of different etiologies may mimic onychomycosis. OBJECTIVE: To determine the prevalence of toenail onychomycosis among patients with leg ulcer and toenail abnormalities attending a dermatology clinic. METHODS: A cross-sectional study was conducted through the analysis of clinical records and results of mycological examination. RESULTS: A total of 81 patients were included, with a median age of 76.0 years. Most ulcers were of venous etiology, followed by those of mixed and arterial pathogenesis. The mycological evaluation confirmed the diagnosis of onychomycosis in 27.2% of the patients. The etiologic agent was a dermatophyte in 59.1% of isolates in nail samples, while Trichophyton interdigitale was the most frequent fungal species (40.9%). CONCLUSIONS: Most toenail abnormalities in patients with chronic leg ulcer were not onychomycosis. This study highlights the importance of systematic mycological examination in these patients, in order to avoid overtreatment with systemic antifungals, unnecessary costs and side effects.
Keywords: Antifungal Agents; Leg ulcer; Microbiological techniques; Onychomycosis

Nail abnormalities are prevalent worldwide. Onychomycosis is the most common cause of toenail deformations in adults, accounting for up to 50% of all nail disorders.[1-5] Onychomychosis has worldwide distribution and is estimated to affect approximately 2-10% of the general adult population in developed countries.[5-9] Predisposition factors are numerous and include increasing age, humidity, occlusive footwear, repeated nail trauma, genetic predisposition, and concurrent disease, such as tinea pedis, diabetes mellitus, poor peripheral circulation, and immunosuppression.[3,5,10,11]

Often a silent and overlooked fungal infection, onychomycosis is a cause of morbidity when associated with wounds and bacterial, infectious complications, particularly in individuals with a compromised health status.[12-15] In addition, it can be a cause of psychosocial stress.[7,13,16] These facts often prompt treatment with antifungals, without previous mycological evaluation. Still, not all dystrophic nails are onychomycosis,[17-19] while inadvertent antifungal treatment has economic costs and is associated with side effects.[20]

Toenail changes are frequently observed among the subset of patients with vascular disease and chronic leg ulcer. However, despite the increasing propensity to toenail fungal colonization and onychomycosis in patients with peripheral vascular disease, nail changes may also be the result of microangiopathy and subsequent chronic ischemia.[17-19]

The aim of the present study was to determine the prevalence of toenail onychomycosis among patients with active leg ulcer and toenail abnormalities.

A cross-sectional study with a nested case-control study was conducted. Further, a convenience sample included all adult patients with chronic active

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leg ulcer and toenail changes, who attended a dermatology clinic during a six-month period, from May to October 2011. Exclusion criteria were: **1)** previous history of systemic or localized disease(s) with known nail involvement; **2)** confirmed diagnosis of toenail onychomycosis in the preceding year; **3)** treatment with systemic or topical antifungals in the preceding six months. Patients' informed consent was required. Data were collected in attendance, through clinical record analysis and patient inquiry, guided by a specific questionnaire that included demographic data, leg ulcer etiology and time of evolution, comorbidities and toenail changes.

Mycological examinations were performed on every patient. According to clinical observation, nail specimens were obtained after scraping the nail plate and/or nail bed with a sterilized scalpel. Whenever clinically suggestive of tinea pedis, sole and interdigital web space skin scrapings were collected. Samples were sent to a laboratory and mycological tests were performed. Direct microscopy observation of fungal structures in fresh material was conducted after immersion in a solution containing potassium hydroxide 40%. Additionally, samples were inoculated in a test tube with a modified Sabouraud medium, supplemented with 0.05 g/L of chloramphenicol and 0.4g/L of cycloheximide (BBL™ Mycosel™ Agar - BD, USA), and incubation was carried out at 24ºC. All cultures were examined weekly for growth for up to four weeks before declaring them negative. Patients with positive direct microscopy and negative culture were retested with new scrapings to exclude false negatives. All negative tests were repeated to validate results. Subcultures, with specific growth mediums, were used to aid in identifying dermatophyte and yeast infections. For the purposes of identification, isolation temperatures were set at 24ºC for filamentous fungi and Candida optimal growth. Each fungal colony growing from inoculate pieces was identified at least to the genus level, through analysis of macroscopic, distinctive colonial traits and/or observation of microscopic, morphologic characteristics in lactophenol blue solution on light microscopy. In the presence of yeasts, a chromogenic agar was used to identify directly *Candida albicans*. Its exclusion prompted the use of the ID32C® system (bioMérieux, France), in order to identify Candida species other than *Candida albicans*. The identification of a dermatophyte, non-dermatophytic mould or yeast confirmed the diagnosis of onychomycosis and/or tinea pedis.

The Statistical Package for Social Studies 20.0 was used for data analysis. $P \leq 0.05$ was considered statistically significant. Results were evaluated by descriptive statistics (using Kolmogorov-Smirnov test of normality) and in the case of nominal variables, the differences were assessed using the χ^2 test. The risk odds ratio (ROR) and a 95% confidence interval (CI) for proportions were calculated using normal approximation to the binomial distribution.

Eighty-one patients with chronic leg ulcer and toenail changes were included, 48 women (59.3%) and 33 men (40.7%), aged 36-91 years (median age 76.0 years, P_{25}; P_{75}=66.5; 83.5). The median evolution time for leg ulcers was 1.5 years (P_{25};P_{75}=0.5;5.0). Regarding etiology, most of the patients had venous leg ulcers (63.0%), followed by mixed (14.8%) and arterial ulcers (11.1%), as documented by Doppler ultrasound. Accordingly, chronic venous insufficiency (CVI) was the most frequent comorbidity (76.5%), and the majority of the patients were overweight or obese (71.6%). Other common associated diseases included hypertension (58.0%), peripheral arterial disease (PAD) (23.5%) and diabetes mellitus (22.2%), with an average of 2.6±1.1 comorbidities per patient. Overall, 56.8% of the patients had more than one toenail abnormality, with 75.3% presenting subungual hyperkeratosis, 40.7% onychauxis, 30.9% total onychodystrophy, 19.8% onycholysis, 6.2% superficial leuconychia, and 4.9% onychogryphosis (Table 1). Eleven patients (13.6%) had clinical signs suggestive of tinea pedis.

Mycological examination was positive in 24 of the 81 patients. Twenty-two patients (27.2%) were diagnosed with onychomychosis (95% CI: 36.9%-75.1%), including 4 patients with concurrent tinea pedis. The remaining two patients were diagnosed tinea pedis, solely. Dermatophytes were the most common cause of onychomycosis (n=13; 59.1% of all isolates). Among dermatophytes, *Trichophyton inter-*

TABLE 1: Clinical data of examined patients (n=81)

Parameter	n	(%)
Comorbidity		
Chronic venous insufficiency	62	76.5
Body Mass Index ≥ 25	58	71.6
Hypertension	47	58.0
Peripheral arterial disease	19	23.5
Diabetes mellitus	18	22.2
Smoking habits	7	8.6
Rheumatoid arthritis	3	3.7
Leg ulcer etiology		
Venous	51	63
Mixed	12	14.8
Arterial	9	11.1
Traumatic	6	7.4
Other	3	3.7
Toenail changes		
Subungueal hyperkeratosis	61	75.3
Onychauxis	33	40.7
Total onychodystrophy	25	30.9
Onycholysis	16	19.8
Superficial leuconychia	5	6.2
Onychogryphosis	4	4.9

digitale was the leading identified species (69.2%), followed by *Trichophyton rubrum* (30.8%). Onychomycosis was due to yeasts in 6 patients (27.2% of all isolates), most commonly caused by *Candida parapsilosis* (66.7%) (Table 2). Patients with superficial leuconychia were more likely to have onychomycosis (ROR 12.9, 95% CI: 1.4-122.8, $P = 0.026$). No statistically significant association was found between other nail changes and presence of onychomycosis.

Table 2: Results of mycological examination

Parameter	n	(%)
Diagnosis		
Onychomycosis	18	22.2
Onychomycosis and tinea pedis	4	4.9
Tinea pedis	2	2.5
Fungal isolates in onychomycosis		
Dermatophytes §	13	59.1
Trichophyton interdigitale	9	40,9
Trichophyton rubrum	4	18.2
Yeasts §	6	27.2
Candida parapsilosis	4	18.2
Candida albicans	1	4.5
Candida lipolytica	1	4.5
Molds	4	18.2
Scopulariopsis spp	4	18.2

Similarly, no statistically significant association was found between demographic and/or clinical data (namely age, gender, comorbidities, ulcer evolution time or etiology) and onychomycosis or fungal agent.

Most leg ulcers are a clinical manifestation of an underlying primary or secondary vascular disease. As verified in clinical practice, these patients frequently present with nail changes suggesting onychomycosis. Nevertheless, other than fungal colonization, patients with leg ulcer may gather predisposing factors for nail abnormalities, such as age and poor peripheral circulation:

a) With respect to age, the normal structure of the nail is altered in the elderly with changes in color, thickness, flexibility and shape, and impairment of function.[4]
b) Vascular abnormalities may bring about onychopathy *per se*.[17-19] Reduced perfusion of the lower extremities results in suboptimal oxygenation, and impaired metabolic exchange of nutrients in the foot. This may not only trigger nail changes and morphological abnormalities, but also hinder nail growth, instigate progression of onychomycosis, and delay / prevent the clearance of infection.[13,21]

The presence of PAD is not only a recognized potential cause for nail dystrophy, but may also predispose to nail fungal infection. A study by Gupta AK *et al.* suggested PAD as an independent predictor of onychomycosis. In their study, mycological evidence of onychomycosis was present in 64.9% of 74 patients with PAP.[21]

Likewise, CVI through venous microangiopathy generates ischemia of the skin, and trophic changes, which include toenail abnormalities, mimicking onychomycosis or predisposing to it.[22-25] Moreover, as both onychomycosis and venous insufficiency are more frequent in the elderly, it is not uncommon to find toenail fungal infection in patients with CVI. Sáez de Ocariz et al. reported a high prevalence of nail changes (61.1%) in 36 patients aged under 60 with CVI.[23] Onychomycosis was the cause of these changes in 59.1%. Shemer et al. documented a higher prevalence (84.1%) of nail deformations among 44 CVI patients, with onychomycosis in 75.7% of the affected nails.[24] In this later study, clinical features were very similar in all patients with nail changes, both for mycotic and nonmycotic pathologies, and no statistically significant difference could be found in the clinical presentation between both groups. This emphasizes the fact that nails have a limited number of reactive patterns to disease, hindering clinical diagnosis.[17-19]

The results from the present study illustrate how few the number of clinical signs of nail disease are and how delusive they can be. All 81 patients enrolled in the study presented with nail signs compatible with the clinical diagnosis of onychomycosis. However, only 27.2% had a positive mycological examination even after repetition of negative results. This low prevalence of onychomycosis, despite being suggestive clinical findings, may reveal the contributory effects of age and vascular disease on nail changes in patients with chronic leg ulcer.

Significantly, data on the present subject are scarce. Moreover, different protocols and populations do not allow a direct comparison with the previously cited studies. However, the contrast between the clinical findings and the results of the mycological examination is transversal to these studies and should be noted. All four studies, including ours, have used mycological examination to diagnose onychomycosis. It is considered the standard diagnostic method for onychomycosis in a clinical setting, since it is inexpensive, noninvasive and accessible.[3] The inconsistency in sensitivity of direct exam and fungal culture is recognized as a possible limitation of the study. Acknowledging this fact, the repetition of negative cultures aimed to reduce the incidence of false-negative results.[26]

As in the general population, most onychomicosis cases were caused by dermatophytes, mainly *Trichophyton interdigitale* and *Trichophyton rubrum*.[1,3,4,9] The risk of onychomychosis was almost 13 times higher in patients with superficial leuconychia. Despite the small number of cases in this study, this could be a more specific reactive pattern to nail mycotic infection.

To our knowledge, this is the first study addressing the prevalence of onychomycosis among patients with chronic leg ulcer and toenail changes. In this subset of patients, most nail abnormalities were not onychomycosis. Regarding costs and potential side effects of systemic treatment, this study further highlights the importance of systematic mycological evaluation in patients with leg ulcer and toenail changes, in order to avoid overtreatment with antifungals. ❑

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REFERENCES

1. Kaur R, Kashyap B, Bhalla P. Onychomycosis - epidemiology, diagnosis and management. Indian J Med Microbiol. 2008;26:108-16.
2. Gupta AK, Ricci MJ. Diagnosing onychomycosis. Dermatol Clin. 2006;24:365-9.
3. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clin Dermatol. 2010;28:151-9.
4. Dias N, Santos C, Portela M, Lima N. Toenail onychomycosis in a Portuguese geriatric population. Mycopathologia. 2011;172:55-61.
5. Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis: an overview of current strategies for monotherapy and combination therapy. J Eur Acad Dermatol Venereol. 2005;19:21-9.
6. Scher RK, Tavakkol A, Sigurgeirsson B, Hay RJ, Joseph WS, Tosti A, et al. Onychomycosis: diagnosis and definition of cure. J Am Acad Dermatol. 2007;56:939-44.
7. Baran R, Sigurgeirsson B, de Berker D, Kaufmann R, Lecha M, Faergemann J, et al. A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement. Br J Dermatol. 2007;157:149-57.
8. Malay DS, Yi S, Borowsky P, Downey MS, Mlodzienski AJ. Efficacy of debridement alone versus debridement combined with topical antifungal nail lacquer for the treatment of pedal onychomycosis: a randomized, controlled trial. J Foot Ankle Surg. 2009;48:294-308.
9. Seebacher C, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. Mycopathologia. 2008;166:335-52.
10. Tosti A, Hay R, Arenas-Guzmán R. Patients at risk of onychomycosis - risk factor identification and active prevention. J Eur Acad Dermatol Venereol. 2005;19:13-6.
11. Mayser P, Freund V, Budihardja D. Toenail onychomycosis in diabetic patients: issues and management. Am J Clin Dermatol. 2009;10:211-20.
12. Crutchfield L, Frescos N, Duncan GJ, Weller C, Woodward M. Prevalence of mycoses in chronic lower limb wounds of people with onychomycosis and/or tinea pedis. Primary Intention. 2005;13:61-7.
13. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C. Toenail onychomycosis: an important global disease burden. J Clin Pharm Ther. 2010;35:497-519.
14. Vanhooteghem O, Szepetiuk G, Paurobally D, Heureux F. Chronic interdigital dermatophytic infection: a common lesion associated with potentially severe consequences. Diabetes Res Clin Pract. 2011;91:23-5.
15. Bristow IR, Spruce MC. Fungal foot infection, cellulitis and diabetes: a review. Diabet Med. 2009;26:548-51.
16. Singal A, Khanna D. Onychomycosis: Diagnosis and management. Indian J Dermatol Venereol Leprol. 2011;77:659-72.
17. Allevato MA. Diseases mimicking onychomycosis. Clin Dermatol. 2010;28:164-77.
18. Tosti A, Iorizzo M, Piraccini BM, Starace M. The nail in systemic diseases. Dermatol Clin. 2006;24:341-7.
19. Gregoriou S, Argyriou G, Larios G, Rigopoulos D.. Nail disorders and systemic disease: what the nails tell us. J Fam Pract. 2008;57:509-14.
20. de Berker D. Clinical practice. Fungal nail disease. N Engl J Med. 2009;360:2108-16.
21. Gupta AK, Gupta MA, Summerbell RC, Cooper EA, Konnikov N, Albreski D, et al. The epidemiology of onychomycosis: possible role of smoking and peripheral arterial disease. J Eur Acad Dermatol Venereol. 2000;14:466-9.
22. Ozkan F, Ozturk P, Ozyurt K, İncı MF, Kalender AM, Bakan B, et al. Frequency of peripheral arterial disease and venous insufficiency in toenail onychomycosis. J Dermatol. 2013;40:107-10.
23. Sáez de Ocariz MM, Arenas R, Ranero-Juárez GA, Farrera-Esponda F, Monroy-Ramos E. Frequency of toenail onychomycosis in patients with cutaneous manifestations of chronic venous insufficiency. Int J Dermatol. 2001;40:18-25.
24. Shemer A, Nathansohn N, Kaplan B, Trau H. Toenail abnormalities and onychomycosis in chronic venous insufficiency of the legs: should we treat? J Eur Acad Dermatol Venereol. 2008;22:279-82.
25. Binaghi F, Cannas F, Fronteddu PF, Pitzus F. Relation between changes in the microcirculation in the capillaries supplying the toenails and the degree of chronic venous insufficiency. Minerva Cardioangiol. 1994;42:163-8.
26. Amichai B, Davidovici B, Trau H, Lyakhovitsky A, Grunwald MH, Shemer A. A rationale for systemic treatment in onychomycosis with negative results on fungal examination. Clin Exp Dermatol. 2011;36:724-7.

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