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Chronic venous insufficiency associated to subclinical onychomycosis

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Abstract
Background: Onychomycosis (OM) and peripheral vascular insufficiency (PVI) are both frequent ailments that share risk factors such as genetic susceptibility, longevity, microvascular alterations, among others. Previous studies have found an association between them, but none has addressed the relation between the vascular disease and subclinical onychomycosis.
Objective: To identify patients with fungal nail invasion and clinically healthy appearing nails. Methods: We included 30 toenail clippings of patients with PVI and clinically healthy appearing nails, processed them in paraffin and PAS stain. These samples were analyzed by an expert dermatopathologist, in search of fungal structures.
Results: Fungal structures invading the nail plate were identified in 10 samples (33.3%). Study limitations this was a pilot study, so the numer of participants is small.
Conclusion: A strong connection existes between these two diseases, even though we didn´t find relation between the presence of fungal structures and the severity of PVI. Previous studies have reported this on clinically evident OM, and now this data in subclinical OM adds up. This field still has many unanswered questions, providing an excellent study opportunity in search of the initial stages of onychomycosis.

Keywords: Chronic venous insufficiency, subclinical onychomycosis, peripheral vascular disease

Introduction

Onychomycosis (OM) is a chronic fungal infection of the nails, primarily caused by dermatophytes, although in rare instances, non-dermatophyte moulds or Candida spp can be responsible for the pathology. It continues to be the most common of nail diseases, and its prevalence has been increasing gradually, particularly in developed countries with large ageing populations. Risk factors include male gender, genetic susceptibility, any type of immunosuppression, diabetes mellitus, and microvascular alterations such as those caused by peripheral artery disease (PAD) and chronic venous insufficiency (CVI). The latter, has studies that show statistically significant relation between this disease and OM coexistence [1]. The widely recognized clinical characteristics of OM are thickening and crumbling of the nail plate, and/or discoloration that varies between white, yellow, brown, blackish or a mixture of all. However, we still dont know how or when exactly this infection starts. Authors have raised the question if the presence of a dematophyte in the nail without classic clinical infection signs (proved by KOH mount or PAS nail clipping) could be considered OM, and thus, controversy exists if treatment should be initiated or not +. A small number of studies are related to subclinical onychomycosis, a term used to classify cases where there are no evident clinical signs of nail fungal infection, but a dermatophyte is demostrated to be present in the clinical sample used for diagnosis, such as KOH mount or PAS stained nail clipping. Two of these studies found 9 and 9.2% of normal apperaing nails were positive to fungal presence [2]. Walling *et al* found that 17% of patients with tinea pedís and apparently healthy nails, resulted positive for fungal structures, and only 1.5% of cases in patients without tinea pedís, supporting the theory that tinea pedís is an important risk factor for OM development [3]. Elbendary *et al*. found 7.5% positive cases in clinically healthy toenails [4]. On the other hand, CVI is a frequent finding with growing incidence in aging populations.

Varicose veins, a very frequent component of CVI, are responsible for 75% of all leg ulcers [5], which makes this disease highly morbid, with an expensive and slow response treatment [6]. Around 9% of the patients may have dystrophyc nails mimicking OM, with deformed nail plate and alterations in the nail´s surface, but are negative to fungal structures. For this reason, adequate diagnosis of OM is fundamental for good clincial practice [7, 8]. Among the most recognized risk factors identified for CVI are male gender, increasing age, smoking, dyslipidemia, diabetes, and hypertension. Almost all of them are also risk factors for OM [9, 10].

Materials and Methods

This is an observational, descriptive, transversal and prospective study, authorized by the ethics and investigation committee of our institution. We examined the toenails of all outpatients that attended the Wound Clinic between March and August 2022 and had diagnosis of peripheral vascular insufficiency (PVI). Those with normal appearing nails (no color change, onycholysis or thickening) and that had not received topical or systemic antifungals for any reason during the last six months, were invited to participate in the study, after signing the informed consent. From the patients that agreed to participate, a nail clipping from the first toenail, either right or left was obtained, and the sample was fixed in 10% formaldehyde, embedded in paraffin and stained with Peryodic Schiff acid (PAS) in an histopathology lab. The samples were analyzed by an expert dermatopathologist.

Results

A total of 30 samples were included: 26 women (86.6%) and 4 men (13.3%) with age range between 36-82 years old (mean 55 years-old). All patients had confirmed PVI and were under treatment for vascular ulcers. Among the most common comorbidities were diabetes mellitus (4 patients), systemic hypertension (2 patients), and overweight or obesity (3 patients), hypertriglyceridemia and hypothyroidism. We found fungal structures in 10 nail samples (33.3%) (Fig 1), hyphae and or/spores that were invading the nail plate, even though no clinical signs of OM were seen. All of them were females, one with DM. The rest had no associated comorbidities (tables 1 & 2). We could not find any relation between the presence of fungal structures and the severity of the PVI.

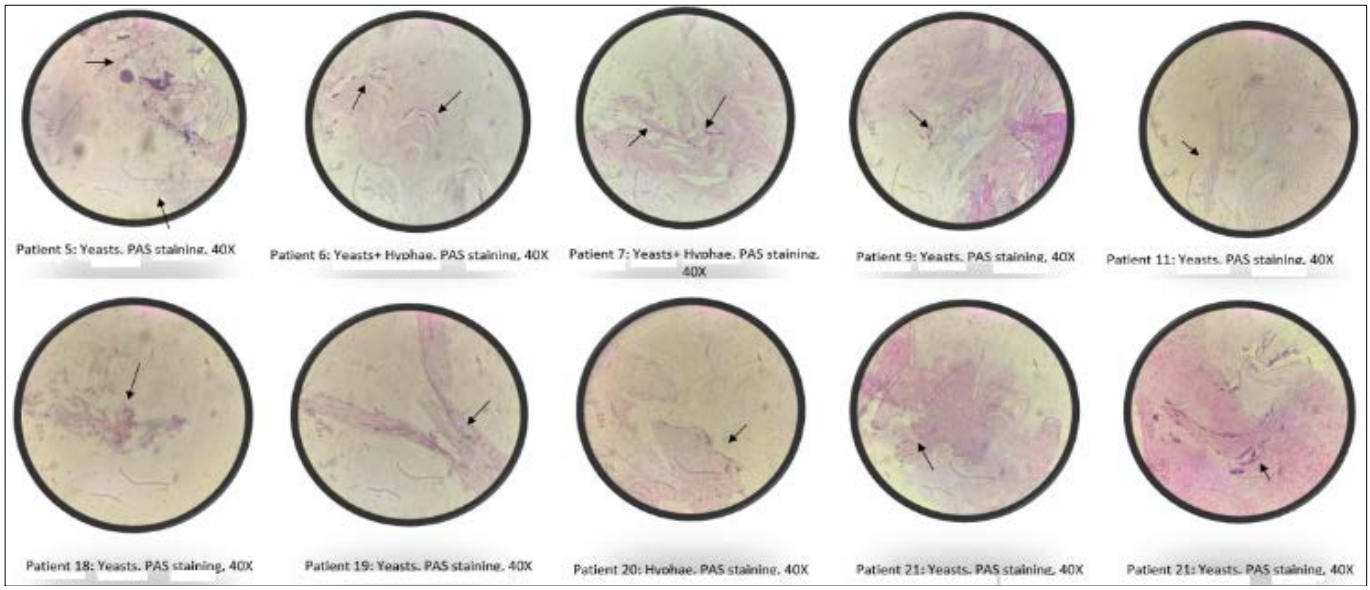

Fig 1: Nail samples with PAS stain

Table 1: results summary

Findings	Patients, n	Percentage
Healthy	20	66.6%
Yeasts	7	23.3%
Hyphae	1	3.3%
Yeasts+ Hyphae	2	6.6%
Total	30	100%

Table 2: patient´s findings in PAS stain

Positive patients	Findings	Comorbidities
Patient number 5	Yeasts	None
Patient number 6	Yeasts+ Hyphae	None
Patient number 7	Yeasts+ Hyphae	None
Patient number 9	Yeasts	None
Patient number 11	Yeasts	Gastritis
Patient number 18	Yeasts	Systemic arterial hypertension
Patient number 19	Yeasts	Hyphothyroidism
Patient number 20	Hyphae	DM2
Patient number 21	Yeasts	Hypertriglyceridemia
Patient number 22	Yeasts	None

Discussion

We chose diagnosing OM with PAS since it has a high sensitivity (92%) and negative predictive value of 77% [3, 7]. These two ailments share an important negative impact in the patients 'quality of life, whilst simultaneously being a big socioeconomic burden. The treatments are expensive for all the material required, as well as time consuming and slow response rates, and work abssenteeism. Venous ulceration treatment is based in compression reaching up to 75% cure rate if adequately applied, but, as the venous incompetence is not reversed, recurrences are common [11]. Also, CVI causes venous hypertension that produce dermatological changes such as stasis dermatitis, lipodermatosclerosis skin, ulcers and onychodystrophia, and this is an environment in which dermatophytes can develop through diverse mechanisms. For example, progressive michroangiopathic changes in nail capillaries [12], large ramified capillaries with thrombi and microvascular obliteration that result in ischemia and edema, with increased permeability and endothelium damage [13].

The purpose of this study is to try to understand more the initial phases of OM and which patients are at higher risk of developing OM, as it is a chronic infection that, although extremely common, its main relevance is often associated to cosmetic issues only. However, we must not forget that some serious complications may be derived from this, such as the dermatophytosis complex, which facilitates bacterial infections that can lead to serious complications in vulnerable patients, such as those with vascular abnormalities [11, 12, 14]. A study found that women in the fifth decade have a higher incidence of both venous ulcers and nail dystrophy, which is in concordance with our results, which were primarily females (86.6%) [13]. Also, they reported cases with onychodystrophy associated to clinically evident onychomycosis in 36.11%, whereas our study found 33.3% as subclinical OM cases. This can be interpreted that more than 60% of the patients with venous ulcers have OM, either clinically apparent or subclinically, besides the known fact that any type of onychodystrophy are in close relation to patients with peripheral vascular diseases [8]. However, another report states that patients with varicose veins had clinically evident OM in only 1.26% [14], which is a low figure overall. To our knowledge no study has addressed before subclinical OM in patients with CVI, where, as our data show, they have a high prevalence. We found that yeasts were more commonly found, which is unexpected, as hyphae are regularly found globally in OM cases worldwide, and in all populations, even in immunosuppressed patients, so this data must be further addressed in future studies. As a final finding, our results dont point to any relation between the presence of subclinical OM and the venous insufficiency severity.

Conclusion

In conclusion, we still have a lot to understand regarding physiopathology of OM, closely related to CVI, the most recurrent vascular condition in Western developed countries. Life style that include sedentarism, smoking and obesity also contribute to increase the number of affected patients [5, 15]. That OM is the most common onychopathy is widely recognized, but we also know that in theory, a fungal organism could possibly be in the nail or skin without invading the host, and thus, without causing an infection, depending mainly on the hosts defense mechanisms and the number of the inoculum [7]. Further studies need to emphazise on the tipping point of colonization to infection, as adequate and timely treatments are our aim.

Conflict of Interest

Not available

Financial Support

Not available

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