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Subungual Space: The Next Frontier

Theresa N. Canavan Lauren V. Graham Boni E. Elewski
Department of Dermatology, University of Alabama at
Birmingham, Birmingham, AL, USA

Dear Editor,

The subungual space is a distinct and clinically relevant part of the nail unit that lies between the nail plate and bed. Although this space is frequently affected by common dermatological conditions, its clinical significance is often overlooked. Diseases affecting the subungual space pose a unique therapeutic challenge. Topical medications are classically applied onto the nail plate; however, diffusion through the nail plate is limited and it is difficult to achieve therapeutic concentrations of medications in the subungual space.

Inflammatory skin conditions, such as psoriasis, affect the subungual space. Psoriasis produces nail changes that result from inflammation in the nail matrix and bed [1]. Inflammation of the matrix leads to pitting, crumbling, and leukonychia in the nail plate. Marked nail bed disease can lead to subungual hyperkeratosis, which, if distal and severe, can contribute to onycholysis. Severe subungual hyperkeratosis can resemble pachyonychia congenita [2]. All variants of pustular psoriasis can also affect the nail bed and matrix through the development of subungual abscesses. Persistent subungual abscesses can produce striking nail dystrophy and potentially result in loss of the nail unit [2]. Nail psoriasis is very recalcitrant to most topical treatments due to the limited ability of topical agents to penetrate the nail plate.

Several other inflammatory skin conditions produce nail changes that result from disease in the matrix and bed. Allergic contact dermatitis can produce psoriasiform nail changes including subungual hyperkeratosis [3]. Prolonged inflammation of the proximal nail bed can lead to subungual hyperkeratosis in both Sézary syndrome and pityriasis rubra pilaris [4].

The subungual space can also harbor microorganisms leading to nail dystrophy. In distal lateral subungual onychomycosis (DLSO), which is the most common type of onychomycosis, the dermatophyte invades distally from the hyponychium and travels proximally in the subungual space and nail bed, leading to onycholysis, subungual debris, and nail plate thickening [5]. In contrast, dermatophytes invade the nail unit from the proximal nail fold in proximal subungual onychomycosis, thereby leading to proximal onycholysis, subungual hyperkeratosis, and proximal nail dystrophy [5]. The pathology in both DLSO and proximal subungual onychomycosis lays in the subungual space and nail bed and not the nail plate.

The subungual dystrophic changes that result from onychomycosis produce a hospitable and accessible environment for bacte-

rial infections. *Pseudomonas aeruginosa* is a common culprit of secondary bacterial infections of the subungual space. Green nail plate discoloration, or chloronychia, results from diffusion of pyocyanin into the nail tissue. As with dermatophyte infection, the pathology of *P. aeruginosa* infection lies in the subungual space; nail plate changes are secondary.

Both inflammatory and infectious disease affecting the subungual space creates a therapeutic challenge as this area is difficult to access with topical medications. Transungual nail penetration is the traditional medication delivery route. However, nail plate diffusion is incomplete, and the disease process is not located in the nail plate. Topically applied medications thus have limited ability to alter the disease process, if they are unable to reach therapeutic levels at the site of active disease.

Topical treatment of onychomycosis requires long treatment courses, and complete clinical and mycological cure is not achieved by everyone. Ciclopirox olamine 8% nail lacquer, efinaconazole 10% solution, and tavaborol 0.5% solution are all topical treatment options that are applied to the plate.

There is an unmet need for the development of novel vehicles and delivery methods to improve the topical treatment of diseases located in the subungual space. Novel vehicles would be useful in the treatment of both inflammatory disorders such as psoriasis and infection such as onychomycosis; both have active pathology in the subungual space and nail bed. Vehicles that allow for enhanced nail plate penetration would improve medication delivery. Some currently available vehicles have a low surface tension, such as efinaconazole 10% solution, which allows for subungual spread. Efficacy may be enhanced when medications with low surface tension vehicles are applied to the hyponychium, as opposed to the nail plate [6–8].

In conclusion, many common diseases affect the subungual space yet the clinical significance of this space is often underappreciated. Topical medications are classically applied onto the nail plate; however, the plate is not the site of disease activity, and diffusion through this structure to the subungual space and nail bed is limited. Prolonged treatments are usually needed for nail diseases, and efficacies can be disappointing. Further research and development of novel vehicles and delivery modalities is needed.

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