A Simple Detection Method of the Resistance to the Treatment of Onychomycosis: A Case Report of *Aspergillus sydowii* Onychomycosis

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A 35-year-old housewife was diagnosed with onychomycosis and treated by oral terbinafine, 250mg/day, for 4 months. Clinically all infected nails improved gradually. However, her left great toe-nail was not improved thereafter. At that time the proximal end of the onychomycotic lesion was marked with surgical blade, and terbinafine therapy was continued for four weeks. However, the onychomycotic nail was not improved, and the scratch mark passed by the proximal end of the infected nail. Therefore, we detected the resistance to the therapy and switched the medication to itraconazole 100 mg/day and then another scratch mark was done at the proximal end of the onychomycotic lesion. After another 2 weeks the infected nail went along with the scratch mark distally, and showed clinical improvement. After 8 weeks therapy of itraconazole, she was cured clinically and mycologically. The fungal culture was identified as *Aspergillus sydowii*. (Ann Dermatol 13(1) 62~65, 2001).

Key Words : Onychomycosis, Resistance, Scratch mark, *Aspergillus sydowii*

Onychomycosis is caused primarily by dermatophytes, *Candida* species, and nondermatophytic molds. Dermatophytes, particularly *Trichophyton rubrum*, are the most common pathogens. The clinical significance of molds is unknown, because they may be colonizing organisms rather than destructive pathogens. It is, therefore, important to identify the pathogen in the array of organisms that may be isolated in culture[1]. Although the newer oral antifungals have been developed, the therapy of onychomycosis may require several months and is associated with a high relapse rate[2]. One study shows that 22.2% of patients with onychomycosis successfully treated with systemic antifungals experienced a relapse. The relapse rate increased from 8. 3% at month 12 to 19.4% at month 24 and to 22.2% at month 36[3]. Usually for the clinician it may be difficult to know whether the applied treatment to onychomycosis patients was effective or not, because clinical improvement was not easily distinguished owing to slow growth rate of the nail. We, herein, report a simple detection method which may reveal a resistance to the treatment through the experience of a case of *Aspergillus sydowii* onychomychosis.

Received July 8, 2000.
Accepted for publication November 6, 2000.
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*This case was presented at the seventh symposium of the Korean Society for Medical Mycology on June 17, 2000

CASE REPORT

A 35-year-old housewife visited the hospital because all her toenail changes for 10 years. Examination revealed a yellowish, hyperkeratotic change of the nails. Fungal hyphae were seen on KOH ex-

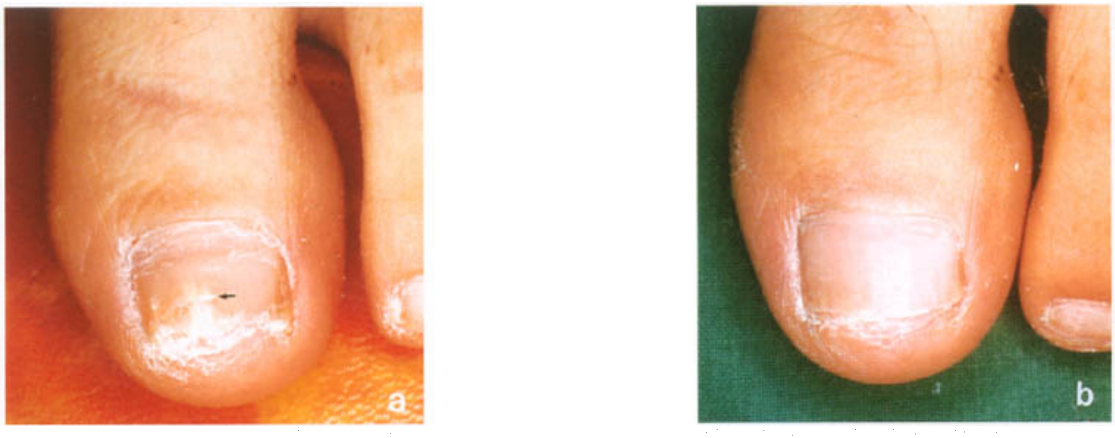

Fig. 1. (a) Scratch mark(arrow) was made on the proximal end of the yellowish onychomycotic lesion before 4 weeks. And now, the mark exceeds the proximal end according to the nail growth, it may mean resistance to the therapy. (b) After 10 weeks' therapy of itraconazole, the nail was cured clinically and mycologically.

Fig. 2. Fungal cultures at 6 colonies were all identical, colony was a blue green color with narrow white margins.

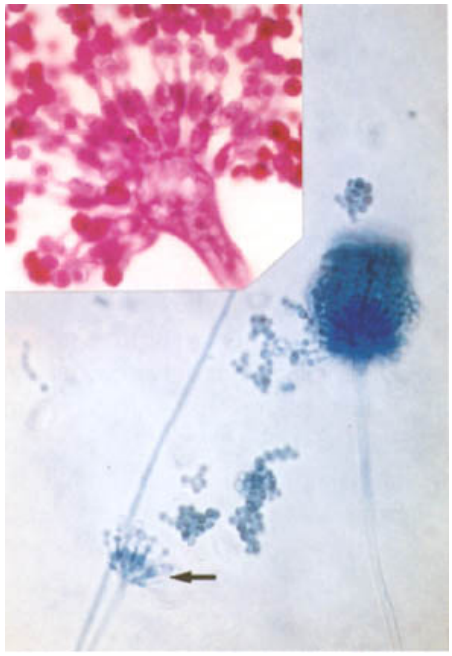

Fig. 3. *Aspergillus sydowii*. There are one globose vesicle and reduced conidial structure resembling *Penicillium*(arrow) (slide culture, cotton blue stain, × 200). (Insert) Detail of head structure (formalin fixed, paraffin embedded, 4 m in thickness section, PAS stain, × 1,000).

amination. Clinically and microscopically it was diagnosed as onychomycosis and treated by oral terbinafine, 250mg/day, for 4 months. Unfortunately, no initial fungal culture was done. Clinically the infected nails were substituted with new fresh nails gradually. However, her left great toe-nail has not improved. At that time KOH preparations revealed many long hyphae. Then fungal cultures using a dental drill were done at 6 colonies on Sabouraud's agar. And also, the proximal end of the onychomycotic lesion was marked with a surgical blade. Terbinafine therapy was continued for four weeks. The onychomycotic nail had not improved, and the scratch mark passed by the proximal end of the infected nail (Fig. 1a). Those findings led us to believe that it meant resistance to the treatment. Therefore, we switched the medication to itraconazole 100 mg/day and then another scratch

mark was done at the proximal end of the onychomycotic lesion. After another 2 weeks, the infected nail went along with the scratch mark distally, and showed clinical improvement and KOH negative. After 8 weeks therapy of itraconazole, she was cured clinically and mycologically (Fig. 1b). Fungal cultures at 6 colonies were all identical, and the colony was a blue green color with a narrow white margin(Fig. 2). Slide cultures were done, and one of these colonies was fixed in formalin, embedded in paraffin, and the block was sectioned 4 m in thickness, finally stained with hematoxylin-eosin and PAS (Fig. 3). We saw many radiating conidial heads, double series of sterigmata, globose conidia, various shapes of vesicles such as globose, spatulate, clavate and reduced conidial structures resembling those in the genus *Penicillium* in PAS stain. So, the colonies were identified as *Aspergillus sydowii* morphologically.

DISCUSSION

Tinea unguium is a common, chronic fungal infection of the nails. The epidemiology and ecology of onychomycosis are complex and little understood. The process of infecting new hosts appears to be facilitated by abrasion, moistening or scratching. The range of interactions between dermatophytes and non-dermatophytes in nails is complex and poorly understood. It would be of clinical interest to know which species found in mixed infections were never able to advance beyond 'secondary colonization', as they would not require specific treatment[4, 5]. Recently, a variety of molds have been isolated from nails as a pathogen[6]. And A. *sydowii* was responsible for 0.49% of nail infections among 2662 infected patients surveyed in Ontario, Canada[7].

Onychomycosis is more difficult to treat than most other dermatophytoses because of the inherent slow growth of the nail. Early one of the authors reported the mean nail growth rate of the great toenail of onychomycosis patients was 0.064 mm/day, and slower than that of normal control[8]. Hence, clinicians may find it difficult to know whether the applied treatment was effective or not. Therefore, it is important to develop a method to detect whether a certain therapy was effective or not. We simply scratched the proximal end of the affected nail plate with a blade, and then observed the relationship between the scratch mark and the proximal end after elapsing of a certain time. If the scratch mark passes by the proximal end, it means resistance to the therapy or fungal defense mechanisms of the host, because the infected nail plate was replaced by a newly growing nail plate when treated by antifungal agents regardless whether fungistatic or fungicidal.

In this case, terbinafine therapy was clinically effective during the initial 4 months, because all toe nails except the left great toenail were clinically improved. Initially her left great toenail also responded to the treatment and clinically improved, however, the nail had not responded after initial improvement. Hence, it was not definite whether it was initially a mixed infection with dermatophyte and nondermatophytic mold, or late infected status of A. *sydowii* on the onychomycotic nail during the treatment period. Our patient responded well to the itraconzole therapy, because A. *sydowii* was known as very sensitive to itraconazole[9]. Anyway, through the simple scratch mark we could know whether the therapy was effective or not. Therefore, we consider that when starting treatment of onychomycosis making the scratch on the proximal end of the onychomycotic nail may be helpful for detecting the resistance to antifungal treatment in onychomycosis.

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