

## Two Cases of Fungal Melanonychia

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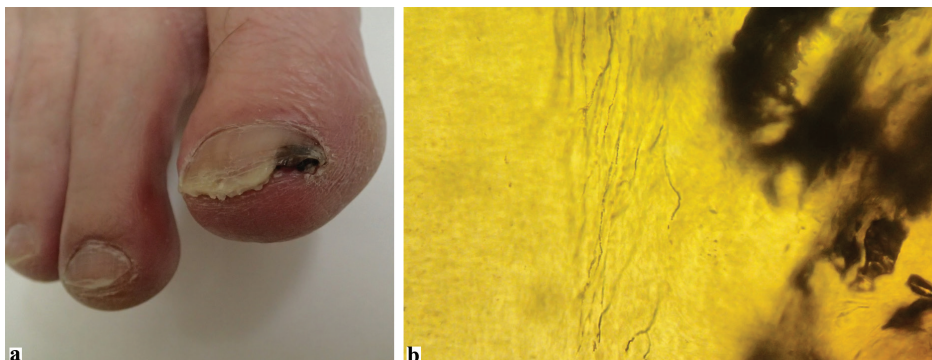
Onychomycosis was initially thought to be predominantly caused by dermatophytes; however, recent research has revealed that onychomycosis caused by non-dermatophytes is also common (1). Onychomycosis usually presents as a white or yellowish turbid nail (2, 3). However, in rare cases, it may present with dark-brown pigmentation, known as fungal melanonychia (4). This is thought to occur because of melanin pigment deposition resulting from phaeohyphomycotic infections such as those from *Curvularia sp.*, *Exophiala sp.*, and *Alternaria sp.*, which contain melanin in their cell walls. However, non-phaeohyphomycotic infections such as those from *Aspergillus sp.*, *Trichophyton sp.*, and *Candida sp.* can also cause fungal melanonychia (5, 6).

In a systematic review of 133 cases, the causative fungi of melanonychia were found to be *Trichophyton rubrum*, *Neoscytalidium dimidiatum*, *Candida spp.*, *Aspergillus niger*, *Fonsecaea pedrosoi*, *Fusarium solani*, *Fusarium oxysporum*, *Exophiala dermatitidis*, *Wangiella dermatitidis*, *Botryosphaeria dothidea*, *Cladosporium spp.*, *Trichophyton interdigitale*, *Aspergillus alternata*, *Scytalidium spp.*, and *Sporothrix spp.* (6). Among these, *T. rubrum* is the most frequent (55%), followed by *N. dimidiatum* (8 %) and *C. parapsilosis* (7%) (6).

Here, we report 2 cases of fungal melanonychia, one caused by mixed *Aspergillus hiratsukae* and *Trichosporon faecale* infection and the other by mixed *Exophiala xenobiotica* and *T. interdigitale*.

### CASE REPORT

The first case involved a 77-year-old man who presented with black longitudinal pigmentation on the right toenail (Fig. 1A). Microscopic findings from foot desquamation and his toenail revealed pigmented materials and long hyphal elements (Fig. 1B). The patient was diagnosed with onychomycosis and tinea pedis.



**Fig. 1.** (A) Clinical photograph: black longitudinal pigmentation on right toenail. (B) Microscopic findings from nail: black pigmented materials and long hyphal elements.

Fungal culture of the black-coloured nails on potato dextrose agar revealed both white (Fig. S1A) and yellowish (Fig. S1B) colonies. Slide culture microscopy of the white colony revealed fungal hyphae and spore clusters (Fig. S2A). Genetic analysis of the white colony, examining the partial nucleotide sequences of  $\beta$ -tubulin and internal transcribed spacer ribosomal deoxyribonucleic acid (ITSrDNA), identified *A. hiratsukae* (Table S1). Slide culture microscopy of the yellowish colony revealed fungal hyphae and yeast-like spores (Fig. S2B); genetic analysis targeting ITSrDNA and 28S ribosomal deoxyribonucleic acid (28SrDNA) identified *T. faecale* (Table SII). Based on these results, the patient was diagnosed with fungal melanonychia, possibly due to combined infection with *A. hiratsukae* and *T. faecale*. The minimum inhibitory concentration (MIC) results of different antifungal ointments against *A. hiratsukae* and *T. faecale* indicated that efinaconazole was effective against both. After 120 days of treatment with 10% efinaconazole, nail pigmentation greatly improved.

The second case involved a 56-year-old man who presented with dark brown longitudinal pigmentation on the left toenail (Fig. 2). Microscopic examination of foot desquamation and nails revealed pigmented materials and fungal hyphal elements, and he was diagnosed with onychomycosis and tinea pedis. Fungal cultures of the dark-brown nails on Sabouraud dextrose agar identified *E. xenobiotica* and *T. interdigitale*. Fungal culture of the pigmented nail on potato dextrose agar revealed a black colony (Fig. S3A); slide culture microscopy revealed fungal hyphae and spores (Fig. S3B), and genetic analysis targeting ITSrDNA and 28SrDNA identified *E. xenobiotica* (Table SIII). *T. interdigitale* was not detected by genetic analysis, but was repeatedly identified by fungal culture tests. From this, the patient was diagnosed with fungal melanonychia, possibly due to combined infection with *E. xenobiotica* and *T. interdigitale*. The MIC results of various antifungal ointments against *E. xenobiotica* and *T. interdigitale* indicated that efinaconazole was effective. After 173 days of 10% efinaconazole treatment, dark-brown nail pigmentation completely resolved.

### DISCUSSION

In these 2 cases, 4 fungi (*A. hiratsukae*, *T. faecale*, *E. xenobiotica*, and *T. interdigitale*) were found to cause melanonychia. *Exophiala sp.*, *Aspergillus sp.*, and



**Fig. 2. Clinical photograph: dark-brown longitudinal pigmentation on left toenail.**

*Trichophyton sp.* have all been reported to cause fungal melanonychia; however, *Trichosporon sp.* have never been reported to induce fungal melanonychia. More than 40 cases of *Trichophyton sp.*-associated fungal melanonychia have been reported, and it is the most common causative fungus. In contrast, *Exophiala sp.* and *Aspergillus sp.*-associated fungal melanonychia are rare; to the best of our knowledge, only 3 cases each of *Exophiala sp.*-associated (7,8) and *Aspergillus sp.*-associated fungal melanonychia (9, 10) have been reported. A similar case of fungal melanonychia from combined fungal infections has also been reported (10). Only 1 case of fungal melanonychia due to *T. interdigitale* has been reported (6); however, cases due to *E. xenobiotica*, *A. hiratsukae*, or *T. faecale*, as observed here, have never been reported.

Three types of melanin have been described in human pathogenic fungi: eumelanin, which is formed from dihydroxyphenylalanine (DOPA)-quinones such as L-DOPA; pyromelanin, derived from homogeneous acid produced by tyrosine catabolism; and allomelanins, formed from nitrogen-free precursors such as dihydroxynaphthalene (DHN) (11). Phaeohyphomycosis, such as *Exophiala sp.*, contains melanin in its cell walls that is produced through the L-DOPA melanin, tyrosine catabolism, or DHN pathways (5, 11). Melanin storage characteristics contribute to fungal melanonychia occurrence (11). Non-phaeohyphomycotic infections, such as those from *Aspergillus sp.* and *Trichosporon sp.* as observed in our cases, are also thought to produce melanin through these pathways (12, 13). *Aspergillus sp.* have been reported to produce melanin through the L-DOPA melanin or DHN pathways (12). *A. hiratsukae* has not been reported to produce melanin pigmentation, but might produce melanin through the same mechanism as other *Aspergillus spp.* *T. faecale* produces melanin through the L-DOPA pathway, resulting in a black polyphenolic heteropolymer (13, 14). The mechanism of melanin production in *E. xenobiotica* has never been discussed; however, *T. interdigitale* may produce melanin by activating melanocytes, similar to other fungi (6). Consequently, non-phaeohyphomycotic infections, such as those from *A. hiratsukae*, *T. faecale*, and *T. interdigitale*, can cause fungal melanonychia.

Three of the fungi (*E. xenobiotica*, *A. hiratsukae*, and *T. faecale*) in these cases have not been previously reported to cause fungal melanonychia. However, in approximately half of the fungal melanonychia cases, fungal cultures are negative, making accurately identifying causative fungi difficult (6), and a wider variety of fungi may induce melanonychia than previously reported. Here, both patients had confirmed infections with both types of fungi; however, it is unclear whether both were involved in melanin production and melanonychia development. Differential diagnoses of fungal melanonychia include subungual melanoma, subungual haemorrhage, drug-induced pigmentation, endocrine diseases, benign melanocytic lesions, and other cutaneous malignancies such as pigmented squamous cell carcinoma (15). As life-threatening conditions must also be considered in differential diagnosis, other possibilities should be carefully investigated and ruled out when fungal melanonychia is suspected.

*The authors have no conflicts of interest to declare.*

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