Non-dermatophyte Mould Onychomycosis in Japan

Hiromitsu Noguchi1, Tadahiko Matsumoto1,2, Utako Kimura2,3, Masataro Hiruma2, Rui Kano4, Takashi Yaguchi5 and Hironobu Ihn6

1 Noguchi Dermatology Clinic
2 Ochanomizu Institute for Medical Mycology and Allergology
3 Department of Dermatology, Juntendo University Urayasu Hospital
4 Department of Veterinary Pathobiology, Nihon University College of Bioresource Sciences
5 Division of Bio-resources, Medical Mycology Research Center, Chiba University
6 Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University

ABSTRACT

The incidence of non-dermatophyte mould onychomycosis has been increasing worldwide for the past several decades, but it is not well recognized in Japan. Recent molecular techniques and phylogenetic analyses contributed to the identification of uncommon and emerging species. We came across 13 (0.5%) cases of non-dermatophyte onychomycosis among a total of 2,591 onychomycosis cases in 106,703 outpatients during the past 5 years (January 2015-December 2019). The cases included 5 patients with Aspergillus species, 4 patients with Fusarium species, and one patient each with Scopulariopsis brevicaulis and Botryosphaeria dothidea, respectively. Botryosphaeria dothidea is closely related phylogenetically to Neoscytalidium dimidiatum. In Japan, at the time of writing this report, there are 26 reported cases of ungual aspergillosis and 18 cases of hyalohyphomycosis caused by Fusarium species. We summarize these cases and report the symptoms and mycological features.

Key words: Aspergillus species, Fusarium species Neoscytalidium dimidiatum, non-dermatophyte mould onychomycosis, Scopulariopsis brevicaulis

Introduction

Non-dermatophyte moulds are filamentous fungi that are regularly found in nature as soil saprophytes and plant pathogens. Moulds can frequently inhabit the nails and are isolated as harmless contaminants in microbiology laboratories. However, they can also invade the nails and cause onychomycosis, and the prevalence of mould infections has been increasing worldwide for the past several decades. Although onychomycosis caused by non-dermatophytes occurs at varying frequency according to geographic location, in developed countries, approximately 10% of onychomycoses are caused by non-dermatophyte moulds. A Canadian survey showed that filamentous fungi were isolated in 3.3% of 2,662 onychomycoses cases. The causative agents included Scopulariopsis brevicaulis in 1.6% (n = 42), Aspergillus species in 0.8% (n = 21), Neoscytalidium dimidiatum in 0.7% (n = 19), Neoscytalidium hyalinum in 0.1% (n = 3), and Fusarium species in 0.1% (n = 2). Non-dermatophyte onychomycosis is uncommon in Japan. A Japanese survey using real-time PCR detected no non-dermatophyte mould in 496 isolates from onychomycosis specimens. We came across 13 (0.5%) cases of non-dermatophyte onychomycosis among 2,591 onychomycoses in 106,703 outpatients during the past 5 years (January 2015-December 2019). We participated in the Japanese survey of dermatomycosis in 2016. Our facility is located in Kumamoto, at the south end of the Japanese archipelago in the temperate region (latitude: 32° north) with an average temperature of 17.2 ± 0.5°C and annual precipitation of 1,986 mm. We herein report the findings from our patients with non-dermatophyte onychomycosis caused by Aspergillus species, Fusarium species, S. brevicaulis, and Botryosphaeria...
dothidea, which is closely related phylogenetically to N. dimidiatum, and summarize the reported cases in Japan.

**Clinical and microbiological diagnosis**

The diagnosis of mould onychomycosis requires a strict correlation between nail abnormalities and mycological findings. We ruled out contamination using 3 or more of these 6 major criteria: identification of the mould in the nail by direct microscopy, isolation in culture, repeated isolation in culture, inoculum counting, failure to isolate a dermatophyte in culture, and histology. Molecular techniques are useful for the rapid identification of etiological fungi. Moreover, a phylogenetic analysis can reveal uncommon and emerging pathogenic fungi from nail samples. The genomic regions that are mostly used for the diagnosis include the internal transcribed spacer (ITS) 1, ITS2, and β-tubulin. Living cultures of isolated pathogenetic fungi were deposited in the culture collection of the Medical Mycology Research Center, Chiba University.

**Ungual aspergillosis**

The genus *Aspergillus* contains many pathogenic agents of non-dermatophyte mould onychomycosis. More than 50% (23/42) of the reviewed epidemiological studies reported that *Aspergillus* species were isolated in 50-100% of the non-dermatophyte moulds. The isolates show a marked geographic variation. Commonly isolated species included *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus sydowii*, *Aspergillus terreus*, and *Aspergillus versicolor*. Toenails were involved 25 times more frequently than fingernails. The predisposing factors include age, gender, duration of diabetes, opportunity for exposure to fungi, and occupation; however, half of the cases lacked any evident risk factors.

In Japan, there were 26 cases of ungual aspergillosis; the mean age of the patients was 51.3 ± 15.6 years (Table 1). Female patients were predominant (female, n = 25; male, n = 1). The listed causative fungi were as follows: *A. niger* (n = 9; 34.6%), *A. terreus* (n = 5; 19.2%), *A. sydowii* (n = 4; 15.4%), *A. flavus* (n = 4; 15.4%), and *A. fumigatus*, *Aspergillus ochraceus*, *A. versicolor*, and *Aspergillus subramanianii* (n = 1; 3.8%). The clinical features depended on the species. *A. niger* caused melanonychia (67%, 6/9) and paronychia (67%, 6/9) on the fingernails (78%, 7/9) (Fig. 1a). *A. flavus* caused invasive aspergillosis. Patients infected with these fungi presented a rare clinical type of proximal subungal onychomycosis (43%, 3/7) on the toenails (71%, 5/7) (Fig. 1b). *A. terreus* was predominantly detected in younger populations (40.5 years), and patients showed superficial white onychomycosis (60%, 3/5) without paronychia (100%, 5/5) on the toenails (80%, 4/5). *A. versicolor* and *A. sydowii* belong to *Aspergillus* section *Versicolores*, patients with these fungi showed distal and lateral subungal onychomycosis (100%, 5/5) on the toenails (100%, 5/5) without underlying disease (100%, 5/5) (Fig. 1c).

We herein present the cases of 3 patients with ungual aspergillosis: (1) A 47-year-old healthy female nurse presented a melanonychia on her right middle fingernail caused by *A. niger* (Fig. 1a); (2) a 23-year-old healthy female retailer presented with proximal subungal onychomycosis on her left big toenail caused by *A. subramanianii* (Fig. 1b); and (3) a healthy 73-year-old female farmer presented with distal and lateral subungal onychomycosis on her right big toenail caused by *A. versicolor* (Fig. 1c). Direct microscopy revealed septate hyphae of uneven thickness and acropetal and intercalary chlamydospodia (Fig. 1d). Histopathologically, periodic acid–Schiff staining showed abundant hyphae branching at angles of approximately 45º (Fig. 1e). Colonies yielded by plate culture on Sabouraud dextrose agar (SDA) at 25ºC appeared black (*A. niger*), yellowish (*A. flavus*, *A. ochraceus*, and *A. subramanianii*), brown (*A. terreus*), and whitish green (*A. fumigatus* and *A. sydowii*). *Aspergillus versicolor* colonies showed various colors (Fig. 1f). Slide culture revealed the characteristic conidial heads of *Aspergillus* species (Fig. 1g).

**Ungual hyalohyphomycosis caused by *Fusarium* species**

*Fusarium* species are found worldwide in all climate zones in soil, in plant debris, and on plants. Next to *Aspergillus*, they are the second leading cause of non-dermatophyte mould onychomycosis in Japan. Hyalohyphomycosis is an infection caused by nonpigmented fungi that form a hyphal element with hyaline or clear walls in tissue. Ungual hyalohyphomycosis caused by *Fusarium* species is uncommon; the frequency is approximately 3% (71/2, 239) in Switzerland. Ungual infection by *Fusarium* species often occurs in the big toes, usually involving injured or defective nails or nail infected with *Trichophyton* species. An immunocompromised patient with acute myelogenous leukemia developed disseminated *Fusarium* hyalohyphomycosis from toenail paronychia was reported.

In Japan, there were 18 cases (male, n = 9; female, n = 9) of ungual hyalohyphomycosis caused by *Fusarium* species; the mean age of the patients was 56.3 ± 17.8 years (Table 2). The affected sites were toenails (n = 12), fingernails (n = 4), and both fingernails and toenails (n = 2). The clinical manifestations included distal and lateral subungal onychomycosis (n = 6; 55%), proximal subungal onychomycosis (n = 5; 45%), and accompanied by paronychia (n = 3; 17%). The pathogens were *Fusarium oxysporum* (n = 6;
| Case No. | Year of report | Age | Sex | Patient’s origin | Underlying disease | Affected site | Subtype | Paronychia (melanonychia) | Treatment | Outcome |
|----------|----------------|-----|-----|------------------|--------------------|---------------|---------|-------------------------|------------|---------|
| 1        | 1980           | 54F | F   | Nagasaki         | SLE                | All finger and toe nails | TDO      | -           | -                   | Improved   |         |
| 2        | 1983           | 35F | F   | Shiga            | -                  | R 4th fingernail    | DLSO     | -           | -                   | -          | Almost cured |
| 3        | 1993           | 24F | F   | Gifu             | -                  | PLE            | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 4        | 1994           | 34F | F   | Kagawa           | -                  | L big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 5        | 1995           | 52F | F   | Nagasaki         | -                  | R big toenail    | DLSO     | -           | A. flavus            | +          | N/A     |
| 6        | 1998           | 66F | F   | Nagasaki         | -                  | All toenails     | DLSO     | -           | A. sydowii           | t-LCZ      | Improved |
| 7        | 1999           | 50F | F   | Ehime            | -                  | L 1st, 2nd & L 3rd fingernails | N/A + A. niger | +           | ITCZ                 | Failure    |         |
| 8        | 2000           | 44F | F   | Tokyo            | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 9        | 2000           | 35F | F   | Nagasaki         | -                  | L & R big toenails | DLSO     | +           | A. terreus(+)        | ITCZ       | Cured   |
| 10       | 2004           | 51F | F   | Osaka            | -                  | L & R big toenails | DLSO     | +           | A. terreus(+)        | ITCZ       | Cured   |
| 11       | 2004           | 56F | F   | Kochi            | -                  | R 3rd & L 4th toenails | DLSO     | +           | A. terreus(+)        | ITCZ       | Cured   |
| 12       | 2005           | 49F | F   | Kanagawa         | -                  | All toenails     | DLSO     | +           | A. terreus(+)        | ITCZ       | Cured   |
| 13       | 2005           | 54F | F   | Kanagawa         | -                  | All toenails     | DLSO     | +           | A. terreus(+)        | ITCZ       | Cured   |
| 14       | 2008           | 68F | F   | Osaka            | -                  | R big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 15       | 2008           | 72F | F   | Osaka            | -                  | R big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 16       | 2008           | 56F | F   | Osaka            | -                  | R big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 17       | 2008           | 33F | F   | Osaka            | -                  | R big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 18       | 2007           | 33F | F   | Osaka            | -                  | R big toenail    | SWO      | +           | A. terreus(+)        | ITCZ       | Cured   |
| 19       | 2009           | 64F | F   | Tokyo            | -                  | L 2nd fingernail | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 20       | 2011           | 57F | F   | Yamaguchi        | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 21       | 2011           | 57F | F   | Yamaguchi        | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 22       | 2015           | 57F | F   | Kumamoto         | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 23       | 2016           | 87F | F   | Kochi            | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 24       | 2016           | 73F | F   | Kumamoto         | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 25       | 2017           | 60F | F   | Me               | -                  | R big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 26       | 2018           | 57F | F   | Kumamoto         | -                  | L big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |
| 27       | 2018           | 33F | F   | Kumamoto         | -                  | L big toenail    | SWO      | +           | A. sydowii           | ITCZ       | Cured   |

**Table 1. Cases of onychomycosis in Japan**

- **TDO:** total dystrophic onychomycosis
- **DLSO:** distal and lateral subungual onychomycosis
- **PSO:** proximal subungual onychomycosis
- **SWO:** superficial white onychomycosis
- **TBF:** terbinafine
- **EFCZ:** efinaconazole
- **ITCZ:** itraconazole
- **LCZ:** lanoconazole
- **LLCZ:** luliconazole
- **ERFCZ:** efinaconazole
- **ML:** male, **FL:** female, **R:** right, **L:** left, **SLE:** systemic lupus erythematosus, **PLE:** protein-losing enteropathy, **-t:** topical, **-i:** injectable, **-E:** efinaconazole, **-T:** terbinafine, **N/A:** not applicable
33%) [22,23], *Fusarium proliferatum* (n = 4; 22%) [22,23], *Fusarium solani* (n = 3; 17%), *Fusarium verticillioides* (n = 3; 17%), and *Fusarium* species (no species-level identification) (n = 2; 11%). Four recent patients (22%) were diagnosed with proximal subungual onychomycosis that involved paronychia (Fig. 2a) [21].

A 45-year-old man presented proximal subungual onychomycosis with paronychia on the left big toenail (Fig. 2a) [21]. He had type 2 diabetes (Hb A1c level, 6.8%). Direct microscopic examination of the nail specimen revealed acropetal and intercalary chlamydoconidia (Fig. 2b) [21]. A histopathological study revealed septate hyphae with uneven thickness and acropetal and intercalary chlamydoconidia (Zoomblue [21] fungal staining solution, original magnification × 400) (e) Histopathology showed abundant hyphae branching at angles of approximately 45° (Periodic acid-Schiff-staining, × 400). (f) *Aspergillus versicolor* had a gray-green suede-like colony with a light brown reverse. (g) Slide culture revealed characteristic conidial heads of the *Aspergillus* species (lactophenol cotton blue, × 400).

**Ungual hyalohyphomycosis caused by Scopulariopsis brevicaulis**

*Scopulariopsis brevicaulis* is distributed worldwide as a soil saprotroph and is the most common etiologic agent of the non-dermatophyte onychomycosis in temperate zones, accounting for approximately 4% (17/431) of cases in Italy [3]. However, it has been a rare etiologic fungus in humans in Japan. Three cases have been documented in Japan since 1968 [24]. Over the past few decades, a considerable number of patients with non-dermatophyte onychomycosis must have been either overlooked or misdiagnosed.

A 44-year-old female homemaker with no underlying disease noticed cinnamon-colored discoloration on her right big toenail (Fig. 3a) [21]. He had type 2 diabetes (Hb A1c level, 6.8%). Direct microscopic examination of the nail specimen revealed acropetal and intercalary chlamydoconidia (Fig. 2b) [21]. A histopathological study revealed septate hyphae and chlamydoconidia (Fig. 2c) [21]. Plate culture of *F. oxysporum* on SDA at 25°C yielded a floccose white colony with pinkish grey reverse (Fig. 2d) [21]. Slide culture revealed verticillate annellidic conidiophores with basipetal chains of conidia (Fig. 2f) [21].
| Case No | Year of report | Age/Sex | Patient’s origin | Underlying disease | Affected site | Subtype | Paronychia | Pathogen | Treatment | Outcome |
|---------|----------------|---------|------------------|--------------------|--------------|---------|------------|----------|-----------|---------|
| 1       | 1964           | 20/F    | Shiga            | (-)                | R big toenail| N/A     | (-)        | F. oxysporum | Onychectomy | Cured   |
| 2       | 1969           | 41/M    | Shiga            | Tinea pedis        | R big toenail| N/A     | (-)        | F. oxysporum | Onychectomy | Almost cured |
| 3       | 1984           | 21/F    | Kanagawa         | Erythermalgia      | All toenails | N/A     | (-)        | F. oxysporum | Thermotherapy | Cured   |
| 4       | 1988           | 81/M    | Osaka            | Subungal carcinoma | R 1st fingernail | N/A     | (-)        | F. oxysporum | N/A        | N/A     |
| 5       | 1997           | 73/F    | Tokyo            | Seleroderma        | L thumbnail, L 3rd & R 4th toenails | N/A     | (-)        | Fusarium spp. | ITCZ        | N/A     |
| 6       | 2005           | 49/M    | Tokyo            | (-)                | R big toenail| DLSO    | (-)        | F. proliferatum | ITCZ        | Cured   |
| 7       | 2005           | 54/M    | Tokyo            | (-)                | L thumbnail, R big toenail | DLSO    | (-)        | F. proliferatum | ITCZ        | Cured   |
| 8       | 2005           | 49/F    | Kyoto            | (-)                | R & L big toenails | N/A     | (-)        | F. solani | ITCZ        | Improved |
| 9       | 2006           | 54/F    | Gifu             | Poor circulation  | R big toenail| DLSO    | (-)        | F. oxysporum | Conservative | Cured   |
| 10      | 2010           | 58/F    | Mei              | (-)                | R thumb nail | N/A     | (-)        | F. solani | t-TBF        | Improved |
| 11      | 2010           | 57/M    | Okinawa          | (-)                | R big toenail| DLSO    | (-)        | F. verticillioides | ITCZ        | Failure |
| 12      | 2011           | 79/M    | Okinawa          | (-)                | L big, 2nd, 3rd, 4th toenails | DLSO    | (-)        | F. verticillioides | t-TBF        | N/A     |
| 13      | 2012           | 74/M    | Kochi            | (-)                | R big toenail| PSO     | (-)        | F. solani | ITCZ        | Improved |
| 14      | 2016           | 73/F    | Kumamoto         | Diabetes           | R big toenail| DLSO    | (-)        | F. proliferatum | t-EFCZ       | Cured   |
| 15      | 2016           | 50/F    | Osaka            | (-)                | R thumb nail | PSO     | (+)        | Fusarium spp. | VRCZ        | Cured   |
| 16      | 2017           | 64/M    | Ishikawa         | (-)                | L 1st fingernail | PSO     | (+)        | F. verticillioides | t-LLCZ       | Improved |
| 17      | 2019           | 45/M    | Kumamoto         | Diabetes           | L big toenail| PSO     | (+)        | F. oxysporum | t-EFCZ       | Cured   |
| 18      | 2020           | 72/F    | Kumamoto         | (-)                | R big toenail| PSO     | (+)        | F. proliferatum | F-RVCZ       | Cured   |

M: male, F: female, R: right, L: left, DLSO: distal and lateral subungal onychomycosis, PSO: proximal subungal onychomycosis, t-: topical, EFCZ: efinaconazole, F-RVCZ: fosravuconazole, ITCZ: itraconazole, LLCZ: luliconazole, TBF: terbinafine, N/A: not applicable
Ungual phaeohyphomycosis caused by Neoscytalidium dimidiatum

Neoscytalidium dimidiatum is the most frequent non-dermatophyte mould pathogen causing onychomycosis in tropical and subtropical regions. In Thailand, N. dimidiatum was the second most common pathogen after dermatophyte and accounted for 17% (41/237) of cases. We do not know why, but N. dimidiatum has never been reported in Japan. The phaeoid fungus N. dimidiatum and dermatophyte Trichophyton rubrum are the most frequently isolated agents causing fungal melanonychia, followed by the genera Alternaria and Exophiala. A survey in Brazil showed that the typical symptom associated with onychomycosis caused by N. dimidiatum was a lateral-distal and lateral-subungual lesion in the big toenail, and melanonychia was observed in 67% (20/30) of all cases. This developed in 27% (3/11) of Caucasian patients and 89% (17/19) of non-Caucasian patients.

We reported the case of an 82-year-old retired Japanese farmer with melanonychia on his right thumbnail caused by a plant-pathogenic fungus, Botryosphaeria dothidea, which is closely related phylogenetically to N. dimidiatum. The sequence of the ITS 1 region of the rRNA gene from the isolate had 95% homology to the N. dimidiatum-type strain CBS 499.66 (accession: FM211432). Direct microscopy revealed branching brown septate hyphae. Histo-pathological examination with periodic acid-Schiff staining revealed black septate hyphae in the nail plate. The thick cell wall appeared to be double-contoured. Plate culture on potato dextrose agar after 7 days at 30°C showed a grayish-white wooly colony with a coal-black-colored reverse. Slide culture showed pigmented broad hyphae and unpigmented branching hyphae.

Treatment of non-dermatophyte mould onychomycosis

Onychomycosis caused by non-dermatophyte mould is intractable and combined therapy with oral itraconazole or terbinafine, chemical and physical removal of the affected nail, and topical application of antifungal agents have been recommended. In the last 5 years, two topical agents (efinaconazole in 2014 and luliconazole in 2016) were approved for the treatment of onychomycosis in Japan.
Fig. 3. (a) Distal and lateral subungual onychomycosis with a cinnamon color on the right big toenail. (b) Numerous oval or lemon-shaped conidia with truncated bases (Zoomblue™ fungal staining solution, original magnification × 400). (c) Septate hyphae and conidia (Periodic acid-Schiff-stain, × 400). (d) Plate culture of *Scopulariopsis brevicaulis*: a buff-colored powdery colony with a pale yellow-brown reverse. (e) Slide culture: verticillate conidiophores with chains of conidia (lactophenol cotton blue, × 400).

Fig. 4. (a) Clinical image at presentation. Melanonychia without Hutchinson’s sign. (b) Direct microscopic examination revealed black branching hyphae. (KOH preparation, original magnification × 400). (c) Histopathology showed black septate hyphae in the nail plate (Periodic acid-Schiff staining, original magnification × 400). (d) Plate culture of *Botryosphaeria dothidea*, which was closely related phylogenetically to *Neoscytalidium dimidiatum*: a grayish-white wooly colony with a coal-black pigmentation on the reverse. (e) Slide culture: pigmented broad hyphae and unpigmented narrow hyphae and chlamydoconidia. (Lactophenol Cotton Blue staining, original magnification × 400).
Efinaconazole shows broad-spectrum antifungal activities in vitro and is expected to be effective for non-dermatophyte onychomycosis caused by Aspergillus species, Fusarium species, and S. brevicaulis. We reported that topical treatment with 10% efinaconazole solution cured non-dermatophyte onychomycoses caused by Aspergillus species, Fusarium species, and B. dothidea. Luliconazole also showed an excellent in vitro activity against non-dermatophyte fungi including Aspergillus species, Fusarium species, N. dimidiatum, N. hyalinum, and Alternaria alternata. Topical treatment with 10% efinaconazole and 5% luliconazole are promising medicines for onychomycosis caused by non-dermatophyte fungi.

Conclusion

Non-dermatophyte moulds have become important etiologic fungi of onychomycosis. Aspergillus species and Fusarium species that cause non-dermatophyte onychomycosis have been frequently isolated in Japan. Through conventional mycological study and advanced genetic analyses, we found two uncommon etiological fungi: S. brevicaulis and B. dothidea. Although non-dermatophyte moulds respond poorly to terbinafine and itraconazole, the topical application of efinaconazole and luliconazole showed excellent antifungal activity along with good clinical results. We believe that serendipity led us to the right path, but always convincing is this pithy saying: “In the field of observation, chance favors the prepared mind (Louis Pasteur, 1854).”

Acknowledgments

This work was partly supported by the National Bio-Resource Project, Japan (http://www.nbrp.jp/) and the Japan Agency for Medical Research and Development, AMED under Grant Number JP19fk0108094.

Conflict of Interest

Self-declared COI content: none

This article was presented at 63rd Annual Meeting of the Japanese Society for Medical Mycology, Chiba, in 2019.

References

1) Maddy AJ, Abrahams JL, Tosti A: Onychomycoses due to non-dermatophytic molds. In Onychomycosis. An illustrated guide to diagnosis and treatment (Tosti A, Vlahovic TC, Arenas R ed), pp.61-71, Springer, Switzerland, 2017.
2) Summerbell RC, Cooper E, Bunn U, Jamieson F, Gupta AK: Onychomycosis: a critical study of techniques and criteria for confirming the etiologic significance of non-dermatophytes. Med Mycol 43: 39-59, 2005.
3) Tosti A, Piraccini BM, Lorenzi S: Onychomycosis caused by non-dermatophytic molds: clinical features and response to treatment of 59 cases. J Am Acad Dermatol 42: 217-224, 2000.
4) Summerbell RC, Kane J, Krajden S: Onychomycosis, tinea pedis and tinea manuum caused by non-dermatophytic filamentous fungi. Mycoses 32: 609-619, 1989.
5) Summerbell RC: Non-dermatophytic molds causing dermatophytosis-like nail and skin Infection. In Laboratory handbook of dermatophytes. A clinical guide and laboratory handbook of dermatophytes and other filamentous fungi from skin, hair and nails (Kane J, Summerbell R, Krajden S, Sigler L, Land g ed), pp. 213-259, Star Publishing Company, Belmont, 1997.
6) Shimeyama H, Satoh K, Makimura K, Sei Y: Epidemiological survey of onychomycosis pathogens in Japan by real-time PCR. Med Mycol 57: 675-680, 2019.
7) Shimeyama H, Sei Y: 2016 Epidemiological survey of dermatomycoses in Japan. Med Mycol J 60: 75-82, 2019.
8) Gupta AK, Drummond-Main C, Cooper EA, Brintnell W, Piraccini BM, Tosti A: Systematic review of nondermatophyte mold onychomycosis: diagnosis, clinical types, epidemiology, and treatment. J Am Acad Dermatol 66: 494-502, 2012.
9) Hirose M, Naguchi H, Yaguchi T, Matsumoto T, Hiruma M, Fukushima S, Ihn H: Onychomycosis caused by Aspergillus subraramianii. J Dermatol 45: 1362-1366, 2018.
10) Haghani I, Shams-Ghaforoki M, Dalimi Asl A, Shokohi T, Hedayati MT: Molecular identification and antifungal susceptibility of clinical fungal isolates from onychomycosis (uncommon and emerging species). Mycoses 62: 128-143, 2019.
11) Bongomin F, Batac CR, Richardson MD, Denning DW: A review of onychomycosis due to Aspergillus species. Mycopathologia 183: 485-493, 2018.
12) Negroni R: Onychomycosis due to Aspergillus species. In Aspergillosis: From diagnosis to prevention 1st ed (Pasqualotto AC ed), pp.961-971, Springer, Heidelberg, 2010.
13) Wijesuriya TM, Kottahachchi J, Gunasekara TD, Bulugahapitiya U, Ranasinghe KN, Neluka Fernando SS, Weerasekara MM: Aspergillus species: An emerging pathogen in onychomycosis among diabetics. Indian J Endocrinol 19: 811-816, 2015.
14) Naguchi H, Hiruma M, Miyashita A, Makino K, Miyata K, Ihn H: A case of fingernail onychomycosis due to Aspergillus flavus. Med Mycol J 57: E21-E25, 2016.
15) Naguchi H, Hiruma M, Matsumoto T, Kano R, Ihn H: Ungual aspergillosis successfully treated with topical efinaconazole. J Dermatol 44: 848-850, 2017.
16) Yamada A, Naguchi H, Sakai H, Sugita T, Hiruma M, Hiruma M: A case of onychomycosis caused by Aspergillus sydowii. Med Mycol J 53: 205-209, 2012. (In Japanese)
17) Matsumoto T, Ajello L, Matsuda T, Szainszlo PJ, Walsh TJ: Developments in hyalohyphomycosis and phaeohyphomycosis. J Med Vet Mycol 32 (Suppl 1): 329-349, 1994.
18) Ninet B, Jan I, Bontems O, Léchéenne B, Jousson O, Lew D, Schrenzel J, Panizzon RG, Monod M: Molecular identification of Fusarium species in onychomycoses. Dermatology 210: 21-25, 2005.
19) Shenoy MM, Shenoy NS: Non-dermatophytic onychomycosis.
In Nail and its disorders 1st ed (S Sacchidanand, Savitha AS ed), pp. 149-157, Jaypee Brothers Medical Publishers, New Delhi, 2013.

20) Bourgeois GP, Cafardi JA, Sellheyer K, Andea AA: Disseminated Fusarium infection originating from paronychia in a neutropenic patient: a case report and review of the literature. Cutis 85: 191-194, 2010.

21) Hirose M, Noguchi H, Matsumoto T, Hiruma M, Yaguchi T, Satoh T: Ungual hyalohyphomycosis caused by Fusarium oxysporum successfully treated with topical efinaconazole. Pract Dermatol 41: 817-820, 2019. (In Japanese)

22) Hattori N, Shirai A, Sugiura Y, Li W, Yokoyama K, Misawa Y, Okuzumi K, Tamaki K: Onychomycosis caused by Fusarium proliferatum. Br J Dermatol 153: 647-649, 2005.

23) Noguchi H, Hiruma M, Matsumoto T, Kano R, Ihn H: Ungual hyalohyphomycosis caused by Fusarium proliferatum in an immunocompetent patient. J Dermatol 44: 88-90, 2017.

24) Kimura U, Hiruma M, Kano R, Matsumoto T, Takamori K, Suga Y: Onychomycosis caused by Scopulariopsis brevicaulis: The third documented case in Japan. J Dermatol 46: e167-e168, 2019.

25) Hay RJ, Ashbee HR: Fungal infections. In Rook’s textbook of dermatology 9th ed (Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D ed), pp. 32.1-32.96, John Wiley & Sons Ltd, Oxford, 2016.

26) Bunyaratavej S, Prasertworonun N, Leeyaphan C, Chaithawon O, Munprasat C, Matthapan L: Distinct characteristics of Scytalidium dimidiatum and non-dermatophyte onychomycosis as compared with dermatophyte onychomycosis. J Dermatol 42: 258-262, 2015.

27) Fineh J, Arenas R, Baran R: Fungal melanonychia. J Am Acad Dermatol 66: 830-841, 2012.

28) Matsumoto T, Matsuda T, Padhye AA, Standard PG, Ajello L: Fungal melanonychia: ungual phaeohyphomycosis caused by Wangiella dermatitidis. Clin Exp Dermatol 17: 83-86, 1992.

29) Cursi IB, Freitas LB, Neves Mde L, Silva IC: Onychomycosis due to Scytalidium spp.: a clinical and epidemiologic study at a University Hospital in Rio de Janeiro, Brazil. An Bras Dermatol 86: 689-693, 2011.

30) Noguchi H, Hiruma M, Matsumoto T, Kano R, Tanaka M, Yaguchi T, Sonoda K, Ihn H: Fungal Melanonychia: Ungual phaeohyphomycosis caused by Botryosphaeria dothidea. Acta Derm Venereol 97: 765-766, 2017.

31) Baran R, Hay R, Haneke E, Tosti A, Piraccini BM: Review of antifungal therapy. In Onychomycosis: The current approach to diagnosis & therapy 2nd ed (Baran R, Hay R, Haneke E, Tosti A ed), pp. 77-129, Informa Healthcare, New York, 2012.

32) Jo Siu WJ, Tatsumi Y, Senda H, Pillai R, Nakamura T, Sone D, Fothergill A: Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. Antimicrob Agents Chemother 57: 1610-1616, 2013.

33) Maeda J, Koga H, Yuasa K, Neki D, Nanjoh Y, Inagaki K, Reangchainam S, Kampirapap M, Makimura K, Harada K, Tsuboi R: In vitro antifungal activity of luliconazole against nondermatophytic moulds. Med Mycol 2019 Nov 23. (E-pub ahead of print)