A Case of Recalcitrant Phaeohyphomycosis of the Face Caused by Exophiala lecanii-corni

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ABSTRACT

We describe a case of recalcitrant phaeohyphomycosis caused by *Exophiala lecanii-corni*, which was previously reported as *Exophiala jeanselmei*, infection. A 63-year-old Japanese woman presented with a 15-year history of multiple pruritic erythematous patches and plaques on the face. Histopathological examination and fungal culture revealed phaeohyphomycosis by *E. jeanselmei*. The attempted treatments included 6 g/day 5-flucytosine (5-FC), 100 mg/day itraconazole (ITCZ), and local hyperthermia. 5-FC was effective initially, but the patient deteriorated after discontinuation. Subsequently, she was referred to our hospital. Histopathological examination showed granuloma with multinucleated giant cells with infiltrating fungal hyphae in the dermis. The causative fungus was finally identified as *E. lecanii-corni* by ribosomal RNA gene analysis. The patient improved after receiving 200 mg/day ITCZ orally for 15 months with local hyperthermia. In the present case, we confirmed the identification of *E. lecanii-corni* as the causative agent by molecular methods. We also emphasize the importance of combination therapy with antymycotic agents and local hyperthermia in phaeohyphomycosis.

Key words: antymycotic agent, *Exophiala jeanselmei*, *Exophiala lecanii-corni*, local hyperthermia, phaeohyphomycosis

Introduction

Phaeohyphomycosis is a rare, cutaneous, subcutaneous, or systemic infection caused by dematiaceous fungi, which exist in the tissue as hyphae. *Exophiala* is a pleomorphic genus comprising at least 40 species and is one of the representative fungi causing phaeohyphomycosis.

*Exophiala lecanii-corni*, which has been distinguished from *Exophiala jeanselmei* by retrospective analysis using molecular methods, is a rare fungus causing phaeohyphomycosis. There are a few case reports of phaeohyphomycosis caused by *E. lecanii-corni*.

Here, we report a rare case of recalcitrant phaeohyphomycosis of the face caused by *E. lecanii-corni*, which had initially been treated according to a diagnosis of *E. jeanselmei* infection, but later recurred. This patient was eventually diagnosed with *E. lecanii-corni* infection confirmed by direct sequencing analysis of the internal transcribed spacer (ITS) region of the fungal rRNA gene.

Case report

A 63-year-old Japanese woman presented with a 15-year history of multiple pruritic dark-colored erythematous patches and plaques on the left face (Fig. 1a). The first skin lesion showed multiple scaly erythematous patches on the right cheek, and then spread to the left cheek. She had received several treatments, including topical steroids and oral and external application of antibiotics, but the eruptions did not improve. Histopathological examination and fungal culture revealed phaeohyphomycosis caused by *E. jeanselmei*. She received 100 mg/day itraconazole (ITCZ) orally for 6 months with no significant improvement. ITCZ was changed to 5-flucytosine (5-FC, 6 g/day) and the skin lesion improved, as documented in a previous report. However, the lesions deteriorated after withdrawal of 5-FC. Several treatments, including re-administration of 5-FC, cryotherapy, and local hyperthermia were tried with no improvement. Subsequently, she was referred to our hospital.

She was employed as an office worker. She had no history...
of facial trauma and no habit of wearing a mask. We did not find fingernail onychomycosis, and she had no history of onychomycosis in the past. She had a past history of pneumonia, meningitis, and phaeohyphomycosis on the neck caused by *E. dermatitidis* during pregnancy at the age of 22 years (Fig. 1b). Details of phaeohyphomycosis on the neck were unclear, except for the initial clinical presentation and histopathological and mycological findings. The fungal isolate at the initial episode was registered as SM 1518 (ATCC 46435) and kept in our department as KMU 5368. Finally, we confirmed this strain as *E. dermatitidis* by sequencing analysis of the ITS region of the rRNA gene.

Laboratory tests, β-D-glucan, CD4/CD8 ratio, and activity of natural killer cells were within the normal range, except for a positive result for antinuclear and anticentromere antibody at a ratio of 160:38. Histopathological examination showed epidermal hyperplasia and marked inflammatory cell infiltration in the dermis with granuloma consisting of histiocytes, lymphocytes, and multinucleated giant cells (Fig. 2a and b). Fungal elements were observed in multinucleated giant cells by periodic acid-Schiff staining (Fig. 2c), which was not observed in the previous report by Yanai et al. The histopathological findings were similar to those of

**Fig. 1.**
a: Multiple pruritic dark-colored erythematous patches and plaques on the left face.
b: Multiple pruritic dark-colored papules aggregated and formed a plaque on the neck.

**Fig. 2.**
a: Histopathological examination in hematoxylin-eosin (HE) stain shows marked inflammatory cell infiltration in the dermis with epidermal hyperplasia.
b: Granuloma consisting of histiocytes, lymphocytes, and multinucleated giant cells with fungal hyphae in the dermis (HE stain).
c: Fungal elements are observed in multinucleated giant cells (periodic acid-Schiff stain).

**Fig. 3.**
a: A giant velvety, shiny colony on potato dextrose agar at 27°C for 14 days, light-brown to olive-green in color. Fungal growth was completely suppressed at 35°C.
b: Slide culture on potato dextrose agar at 27°C for 14 days shows pale-brown, ellipsoidal, large conidia on the sides and tips of the septate hyphae.
phaeohyphomycosis on the neck at the age of 22.

Gross findings of colonies grown on potato dextrose agar at 27°C for 14 days showed light-brown to olive-green velvety colonies (Fig. 3a). Fungal growth was completely suppressed at 35°C. Slide culture on potato dextrose agar at 27°C for 14 days showed pale-brown, ellipsoidal, large conidia (3.3-5.9 x 1.7-2.5 µm, mean 4.6 x 2.0 µm) on the sides and tips of the septate hyphae (Fig. 3b). Sequencing analysis of the ITS regions of the rRNA revealed 100% homology with a registered sequence of an E. lecanii-corni strain (CBS123.33).

The patient received 200 mg/day ITCZ orally for 15 months with local hyperthermia with a disposable heat pack, and the lesion markedly improved (Fig. 4). Since the patient was too far away to visit our hospital regularly, she requested to be followed up by her previous doctor. We conducted a follow-up interview by telephone one year after the last visit to our hospital and confirmed that there were no symptoms or worsening of the lesion, and she reported that local hyperthermia was being continued.

Discussion

E. lecanii-corni, a melanized dimorphic fungus, was initially discovered associated with the European fruit lecanium scale and named Torula lecanii-corni(2). Subsequently, strains of E. lecanii-corni were isolated from cutaneous phaeohyphomycosis on humans by De Hoog et al. in 1994(3), which is the first report describing E. lecanii-corni as a causative agent of phaeohyphomycosis.

E. lecanii-corni has been isolated from aquatic environments in human habitats, such as sludge in bathroom drainpipes and swimming pools(4,5), and is responsible for 7% of clinically isolated Exophiala infections in the United States(6). E. lecanii-corni infects the lungs and other internal organs, skin lesions, and paranasal sinuses, similar to other Exophiala species(7).

There have been five cases of phaeohyphomycosis reportedly caused by E. lecanii-corni (Table 1)(3,6-9). Representative clinical symptoms were pruritic erythematous patches and/or nodules on the exposed areas, such as the finger, forearm, and face. Cerebral and visceral infections have not been reported in previous cases. Patients received terbinafine (TBF), ITCZ, fluconazole (FLCZ), and voriconazole (VRCZ) for 2-6 months orally without surgical treatment(3,6-9).

In the present case, surgical treatment was not performed because of multiple lesions on the face, and 200 mg/day of ITCZ was more effective than 5-FC or 100 mg/day of ITCZ. ITCZ and VRCZ were reported to inhibit the growth of Exophiala species in vitro experiments(8). Based on previous reports and the present case, TBF and ITCZ are candidates for a first-choice drug. However, if they are ineffective, VRCZ or a combination of two antimycotic agents may be recom-

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**Table 1. Case reports of phaeohyphomycosis caused by Exophiala lecanii-corni**

| Case | References | Age /gender | Underlying disease | Prior trauma | Duration | Site | Symptoms | Used antimycotics (months) | Local hyperthermia | Outcome |
|------|------------|-------------|-------------------|--------------|----------|------|----------|---------------------------|------------------|---------|
| 1    | de Hoog GS et al. | 47/F | MPA, DM, RF (PSL15mg/day, Cyclosporine 100mg/day) | 1 week | the Third finger | Cheek | Pruritic brown macules | TBF 125mg (unknown) | Improved |
| 2    | Watanabe et al. | 74/M | MPA, DM, RF (PSL15mg/day, Cyclosporine 100mg/day) | 1 week | the Third finger | Subcutaneous abscess | TBF 125mg (2) | Cured |
| 3    | Tsujioka et al. | 56/F | DM | 3 years | Bilateral cheeks | Forearm | Sclerotic papules | ITCZ 200mg (6) | Cured |
| 4    | Lee KC et al. | 76/M | DM | 18 months | Forearm | Pruritic maculopapular | TBF 125mg (3) → FLCZ 150mg (4) | Cured |
| 5    | Saito et al. | 45/F | DM | 5 years | Buttock | Multiple brownish dark-red nodules | ITCZ 200mg (3.5) → VCZ 600mg (4) | Improved |
| 6    | Present case | 63/F | History of phaeohyphomycosis | 15 years | Bilateral cheeks | Pruritic maculopapular | ITCZ 200mg (6) → 5-FC → ITCZ 200mg | Cured |

MPA: microscopic polyangitis, DM:diabetes mellitus, RF: renal failure, SLE: systemic lupus erythematosus

PSL: prednisolone, TBF: terbinafine, ITCZ: Itraconazole, FLCZ: Fluconazole, VRCZ: Voriconazole, 5-FC: Flucytosine
**Phaeohyphomycosis is intractable and treatment has not been established. Local hyperthermia has been used in combination with oral antifungal therapy in a previous report**\(^4\). It is reported that the maximum growth temperature of *E. jeaneselmei* and related species is 35-37°C\(^{15, 15}\). Tsujioka et al. reported a case of phaeohyphomycosis caused by *E. lecanii-corni* showing resolution of eruptions every summer\(^3\). The fungal growth of their strain was remarkably suppressed at 33 °C and was not observed at 37°C, similar to our strain, and is characteristic of *E. lecanii-corni*. These results indicate that local hyperthermia is efficacious in inhibiting the growth of *E. lecanii-corni* because disposable chemical pocket warmers, which are very popular in Japan and are now usually used in local hyperthermia, increase the surface skin temperature to 40-42°C\(^{16, 17}\) and consequently inhibit the growth of *E. lecanii-corni*.

The combination treatment of oral antymycotics and local hyperthermia in our case seemed to be quite effective against the lesions. The patient continued only local hyperthermia after discontinuing oral antymycotics, and the lesion remained in good condition. In the present case, the lesion extended to the level of the subcutaneous tissue at a depth of 2 mm. Naka et al. reported that the tissue temperature at a depth of 3-4 mm increased to 40.5 °C after application of a pocket warmer\(^{19}\). Therefore, in our case, local hyperthermia is believed to have maintained a sufficient temperature to prevent fungal growth in the tissue.

The present case was previously reported as phaeohyphomycosis by *E. jeaneselmei*\(^{20}\). Correct identification of *Exophiala* species by morphological and physiological parameters is very difficult, especially for *E. jeaneselmei*, as many of these fungi are morphologically similar but consist of genetically different strains\(^6\). Recently, *Exophiala* species were accurately identified using molecular methods, particularly sequencing of the ITS regions of the rRNA gene\(^{18-20}\), which allowed *E. jeaneselmei* to be distinguished from similar species.

The paucity of reported cases of *E. lecanii-corni* infection may be due to the recent identification of the strain and the need for identification based on molecular biology. The actual number of *E. lecanii-corni* infections may be much higher. It should be noted that related *Exophiala* species may be the true causative agent for previous case reports of *E. jeaneselmei* infections identified without using molecular methods.

Our patient was a healthy individual with no evidence of immunosuppression. However, one of the interesting aspects of this patient is that she had a history of phaeohyphomycosis of the neck. We initially suspected that the causative agent of phaeohyphomycosis of the cheek was derived from the previous phaeohyphomycosis of the neck, but the eruption of the neck had disappeared when she was referred to our hospital. As the fungal isolate from the neck was kept in our department, we examined the differences between the strains from the neck and those from the cheek based on molecular biology. As a result, we found that the causative fungus in the neck was *E. dermatitidis*, and we concluded that the *E. lecanii-corni* infection was newly developed in the cheek after a long interval after the improvement of the *E. dermatitidis* infection. Systemic dissemination did not occur despite the long duration of the disease, which is probably because the patient was not immunosuppressed and because the causative agent was *E. lecanii-corni*.

Recently, it was reported that *CARD9* (caspase recruitment domain-containing protein 9) mutations are associated with certain dematiaceous fungal infections in healthy patients with phaeohyphomycosis\(^{11}\). Patients with autosomal recessive *CARD9* mutations are predisposed to recurrent mucocutaneous or invasive candidiasis\(^{21, 22}\), superficial and deep dermatophytosis caused by *Trichophyton* species\(^24\), and phaeohyphomycosis caused by *Phialophora verrucosa* and *Exophiala* species\(^{25-27}\).

We did not find fingernail onychomycosis or mucosal candidiasis, but there was a history of phaeohyphomycosis caused by two different *Exophiala* species at different sites, which led to the suspicion of primary genetic immunodeficiency to dematiaceous fungi. Wang et al. proposed an examination of *CARD9* deficiency in healthy patients with recurrent phaeohyphomycosis\(^{21}\).

Our patient may have a mutation of *CARD9* or other genetic abnormalities, which might be involved in the repeated infection by dematiaceous fungi. Unfortunately, she stopped coming to our hospital, and we could not examine genetic abnormalities, including *CARD9*.

We emphasize that patients with phaeohyphomycosis should continue to be treated until they are completely cured. Surgical treatment is the most likely curative treatment, but if not possible, a combination of antymycotic agents with local hyperthermia is recommended. As the number of cases with *E. lecanii-corni* infection increases, more details of the clinical course and the best treatment will become clear.

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**Conflicts of interest**

Nothing to declare.

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