



## Case report

Phaeohyphomycosis due to *Exophiala spinifera* greatly improved by ALA-PDT: A case report

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## ABSTRACT

An 80-year-old woman complained of painful erythema, papules, nodules on her right wrist for 9 months. Granuloma and inflammatory infiltrates with septate fungal hyphae were observed in pathological sections. Growth of dematiaceous fungus on SDA was confirmed to be *Exophiala spinifera* by microscopic appearance and ITS rDNA sequencing. The diagnosis of phaeohyphomycosis due to *E. spinifera* was established. The patient had a poor response to oral itraconazole (200 mg/d) combining with terbinafine (250 mg/d) for 6 weeks. Then, following three courses of ALA-PDT, used as adjuvant therapy, skin lesions greatly improved and remained stable after 3 months follow-up. The case suggests that ALA-PDT is an effective adjuvant treatment option for patients with recalcitrant local subcutaneous fungal infection.

## 1. Introduction

Phaeohyphomycosis encompasses all cutaneous, subcutaneous and systemic infections caused by melanized fungi characterized by melanin in their cell walls. The hallmark of this disease is the presence of brown yeast-like cells and/or hyphal elements in tissue without sclerotic cells. Phaeohyphomycosis is caused mostly by *Wangiella dermatitidis*, *Alternaria* sp., and *Exophiala jeanselmei* and rarely by *Exophiala spinifera* [1]. To date, no more than 40 cases caused by *Exophiala spinifera* have been reported in the English literature [1–4].

The treatment of phaeohyphomycosis includes mainly long-term orally administered antifungal agents [1]. However, some patients have poor responses to antifungal agents. A combination with surgery, cryotherapy or other therapy is necessary for these patients. Photodynamic therapy (PDT) is an innovative antimicrobial approach that combines a non-toxic dye or photosensitizer (PS) with harmless visible light. As some PSs bind rapidly and selectively to microbial cells, PDT has been proposed as an alternative approach for localized infections, such as those caused by bacteria, parasitic protozoa, fungi, yeast, and virus infections [5]. Here, we report a case of phaeohyphomycosis due to *E. spinifera* that was greatly improved by ALA-PDT.

## 2. Case report

An 80-year-old woman presented to our outpatient clinic complaining of painful erythema, papules, and nodules on her right wrist for 9 months. Dermatological examination showed erythema, papules, and several nodules (2 × 2 cm) with purulent discharges on her right wrist and forearm. Routine blood test investigations were normal. Flow cytometry showed a decreased number of total T cells [509 cells/μL (normal: 690–2540)] and T helper cells [298 cells/μL (normal: 410–1590)], which indicated that the patient was in a state of immunosuppression. The patient was a farmer, and she did not recall any history of trauma or puncture to the wrist. She had a history of rheumatoid arthritis for 5 years and had taken oral “Cao qinghua capsules” (A kind of Chinese traditional herb that is considered to contain the glucocorticoid) for 1 year.

Direct examination (10% KOH) of the purulent discharge revealed irregular and septate hyphae (Fig. 1A). Histopathology showed granuloma and inflammatory infiltrates including neutrophils, multinuclear giant cells, lymphocytes, plasma cells, and histiocytes along with septate fungal hyphae (Fig. 1B). Culture on Sabouraud dextrose agar containing chloramphenicol and gentamicin incubated at 25 °C showed growth of dark black, mucoid yeast-like colonies initially turning downy in texture (Fig. 1C inset). Slide culture after 2 weeks of

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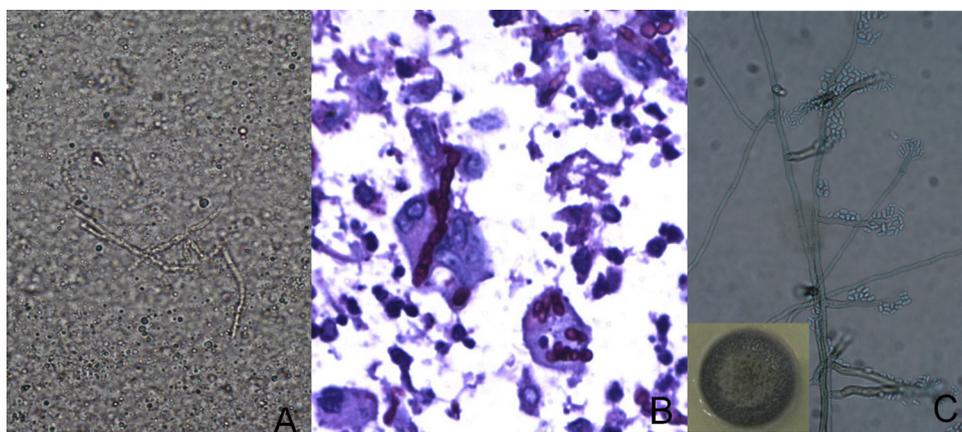
E-mail address: [gdnpcyf@126.com](mailto:gdnpcyf@126.com) (Y. Chen).

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**Fig. 1.** A Direct microscopic examination (KOH 10%) of the purulent discharge revealed irregular and septate hyphae. ( $\times 400$ ).

**B** Histopathology showed brown septate hyphae in macrophage. (Periodic acid-Schiff (PAS) stain,  $\times 400$ ).

**C** Spine-like conidiophores with thick walls bearing clusters of ellipsoidal conidia arising apically or laterally at right or acute angles. (Lactic acid phenol cotton blue staining,  $\times 1000$ ).

**C Inset:** Downy colony of *E. spinifera* on SDA for two weeks.

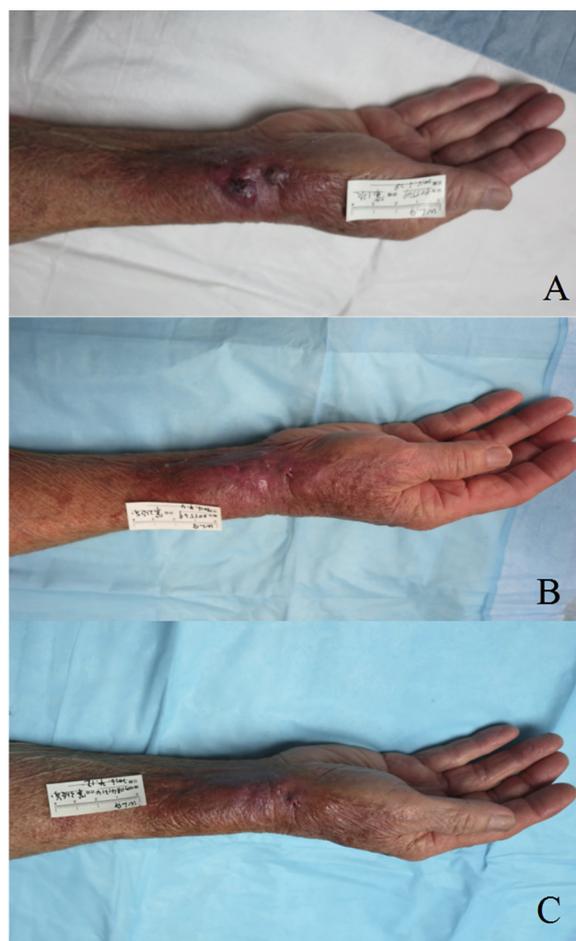
incubation at 25 °C revealed spine-like conidiophores with thick walls bearing clusters of ellipsoidal conidia arising apically or laterally at right or acute angles (Fig. 1C). Cardinal growth temperatures of the strain were optimal at 27 °C, scant at 37 °C, and no growth at 42 °C. Internal transcribed spacer (ITS) rDNA sequences of the strain had 98% identity with *E. spinifera*. The diagnosis of phaeohyphomycosis due to *E. spinifera* was established.

Oral itraconazole (200 mg/d) combining with terbinafine (250 mg/d) was administered for 6 weeks, but the patient had a poor response. Therefore, PDT irradiation with 20% 5-aminolevulinic acid (ALA) (Shanghai Fudan-Zhangjiang Biopharmaceutical Co. Ltd., Shanghai, China) was applied 3 times at an interval of 1 week. Briefly, the abscess was rinsed with normal saline, freshly prepared 20% ALA cream was applied to the lesion and incubated in dark for 4 h. After incubation, 633 nm red light with an intensity of 120 mW/cm<sup>2</sup> irradiance was delivered for 25 min. There were no obvious irradiation-related adverse events except mild burning and temporary pain. After 3 ALA-PDT applications, the papules and nodules almost disappeared, with only hyperpigmentation remaining (Fig. 2A–C). The patient could not afford more times of ALA-PDT since it was very expensive and not covered by medical insurance. During and after ALA-PDT, she continued to take oral itraconazole and terbinafine and remained stable after 3 months follow-up. Repeated mycology cultures of skin lesions showed no fungi growing up.

### 3. Discussion

*E. spinifera* is a dematiaceous fungus that has a widespread geographic and ecological distribution (e.g., organic wastes, plant debris and soil). Our patient had no history of trauma, but she was an elderly farmer in an immunosuppressed state. We suspected that she probably had been contaminated with *E. spinifera* from soil or plant debris and infected by an undetectable minor injury. Since *Exophiala* species have similar morphologies, ITS sequencing is the gold standard for identifying *E. spinifera*. In our case, *E. spinifera* was identified according to morphology and rDNA ITS sequencing.

At present, no standard antifungal therapy can be recommended to treat phaeohyphomycosis [6]. Itraconazole is the most commonly used therapy (20 cases) and the most effective antifungal drug, as complete recovery was obtained in 9 cases and improvement or stability in 7 cases [1]. However, after 6 weeks of combination antifungal agents, the skin lesion of our patient did not improve remarkably. Considering her advanced age and large skin lesions, we tried to use PDT as an adjuvant therapy. PDT-mediated clearance of bacterial infections not only kills bacteria but also attracts and accumulates neutrophils into infected regions [5]. To our knowledge, the effect of PDT on *E. spinifera* has not been previously reported. In our case, ALA-PDT worked synergistically with oral antifungal agents, the skin lesions greatly improved only after



**Fig. 2.** A Erythema, papules, and nodules on her right wrist after the first application of ALA- PDT.

**B** The Papules and nodules flattened after the second application of ALA- PDT.

**C** The papules and nodules almost disappeared with hyperpigmentation retaining after the third application of ALA- PDT.

3 applications without obvious side effects. In our opinion, ALA-PDT is a safe treatment for local phaeohyphomycosis and can improve clinical symptoms in a short time. We suggest using of PDT as an effective adjuvant treatment option combining with antifungal agents for patients with recalcitrant local subcutaneous fungal infection.

### Declaration of Competing Interest

The authors declare no conflicts of interest.

### Acknowledgment

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