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Extensive Deep Dermatophytosis Cause by *Trichophyton rubrum* in a Patient with Liver Cirrhosis and Chronic Renal Failure

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Abstract Dermatophytes are the main pathogen of superficial skin fungal infections. On rare occasions, they can cause deep and extensive infections, especially in immunocompromised hosts. We reported a 48-year-old patient with liver cirrhosis and chronic renal failure who developed an extensive deep dermatophytosis with possible hematogenous dissemination. Skin histopathology showed extensive involvement of hair follicles and dermis by fungal elements. The pathogen was cultured from both skin biopsy specimen and central venous line. It was identified as *Trichophyton rubrum* by morphology and further conformed by sequencing of internal transcribed spacers of ribosomal DNA. The patient died quickly before the identification was available.

Keywords Extensive · Deep · Dermatophytosis · *Trichophyton rubrum* · Liver cirrhosis · Chronic renal failure

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Introduction

Dermatophytosis is a common disease in dermatologic clinical practice, which can cause various forms of tinea. The typical features of tinea are scaly and erythematous papule to patches with active borders. Many dermatophytes have been reported to be the pathogens, and the incidence depends on the disease types and geographic regions. *Trichophyton rubrum* is the most prevalent dermatophyte species all over the world. It is an anthropophilic fungus which can cause all types of tinea, such as tinea pedis, onychomycosis, tinea corporis, tinea cruris, and tinea manuum [1]. It can also infect scalp hairs and result in endothrix as well as ectothrix tinea capitis. In uncommon occasions, it can cause severe, aggressive, and widespread lesions, especially when the hosts are under immunosuppressive state. Different from those of superficial

infections, the clinical presentations are atypical and bizarre, such as dusky-red infiltrated plaques, nodules, cysts, abscesses, and ulceration with widespread involvements [2–8]. We report a case of extensive deep dermatophyte infections of the head and neck with possible hematogenous dissemination caused by *T. rubrum* in a patient with liver cirrhosis and chronic renal failure.

Case Report

A 48-year-old male had a medical history of HBV- and HCV-related liver cirrhosis, Child-Pugh class B, esophageal varices after ligation surgery, peripheral arterial occlusive disease over bilateral lower limbs, and end-stage renal disease under regular hemodialysis. On April 27, 2012, he was sent to the emergency room due to high fever and short of breath. The chest X-ray showed prominent bilateral pulmonary filtration and edema. The physical examination showed multiple eroded wounds over the right thigh and mild swelling over the right ankle. Under the impression of pneumonia, septic shock with unstable hemodynamic status, and cellulitis of right ankle, he was admitted to the intensive care unit of our hospital on April 28, 2012. In the ICU, he received treatment for a combination of piperacillin and tazobactam (Tazocin^{TM}) 2.25 g intravenous every 8 h for pneumonia from April 28 to May 17, 2012. Meanwhile, blood transfusion and colloid fluid were given to maintain hemodynamic stability. Methicillin-resistant staphylococcus aureus (MRSA) was isolated from the right thigh wounds, and teicoplanin 400 mg was added per 12 h for three times and then every 3 days from April 28 to May 17, 2012. On May 5, 2012, skin rashes appeared on his abdomen and inguinal area, and the dermatologist was consulted. The tentative diagnosis was an allergic reaction, and topic steroid was prescribed. The skin lesions subsided completely after topical steroid treatment. The infection and patient's condition stabilized gradually after treatment, and he was transferred to general ward on May 7, 2012.

On the next day after transferal, new skin rashes, which were totally different from that of the previous episode on abdomen and inguinal areas, appeared on the patient's face. The rashes responded to the topical steroid prescribed by the internal medical physician poorly and soon extended to neck and scalp. The dermatologist was consulted again to evaluate these new rashes on May 16, 2012. Upon this consultation, there were large dusky-red verrucous, papuloplaques and nodules scattered on the patient's forehead, periorbital area, cheeks, mandible, and neck. The lesions had a relative well-defined border and were covered with white scales and hemorrhagic crusts (Figs. 1, 2). A skin biopsy was taken from his right temporal area under the impression of granulomatous dermatitis or atypical microbial infections. The specimen was also sent for histopathologic examination and culturing of bacteria, mycobacteria, and fungi. The histopathology showed a dermal and periadnexal mixed inflammatory cell granulomatous inflammation. The hair follicles were dilated and filled with round fungal spores and septate hyphae. There were also dense branching fungal hyphae with large round chlamydospores infiltrates in the dermis (Fig. 3). The Gram's stain and acid fast stain for bacteria and mycobacteria were negative. Tissue culturing on brain heart infusion (BHI) agar grew a mold, and culturing results for bacteria and mycobacteria were negative.

Due to persistent fever, blood culture was performed and central venous catheter (CVP) was removed and sent for culture. No microorganism grew from the blood sample, but a mold grew from the CVP tip culture. Anidulafungin (Eraxis^{TM}) 200 mg intravenous once and then 100 mg intravenous once per day were given from May 20 to 27, 2012 under the initial impression of systemic aspergillosis. The patient, however, experienced short of breathe and was transferred to the ICU again due to unstable hemodynamic. The patient's clinical condition deteriorated rapidly. He refused to receive resuscitation and expired unfortunately at 10 days after transferring to ICU. No autopsy was performed.

The identification of molds from skin biopsy and CVP tip cultures was reported after patient's death. They are a same fungus. It had a whitish fluffy surface and red reverse on potato dextrose agar. The slide culture of the fungus under microscopy showed microconidia with variable size arrange alongside the hyphae. A few intercalary chlamydospores could be seen. The isolate from skin biopsy was subjected to molecular identification by amplifying and sequencing of the ITS1-5.8S-ITS2 regions of ribosomal DNA (rDNA) with primer pairs of ITS1/ITS4. The sequence was 100 % identical to CBS 392.58 of *T. rubrum* with 100 % coverage. The place where CVP inserted was

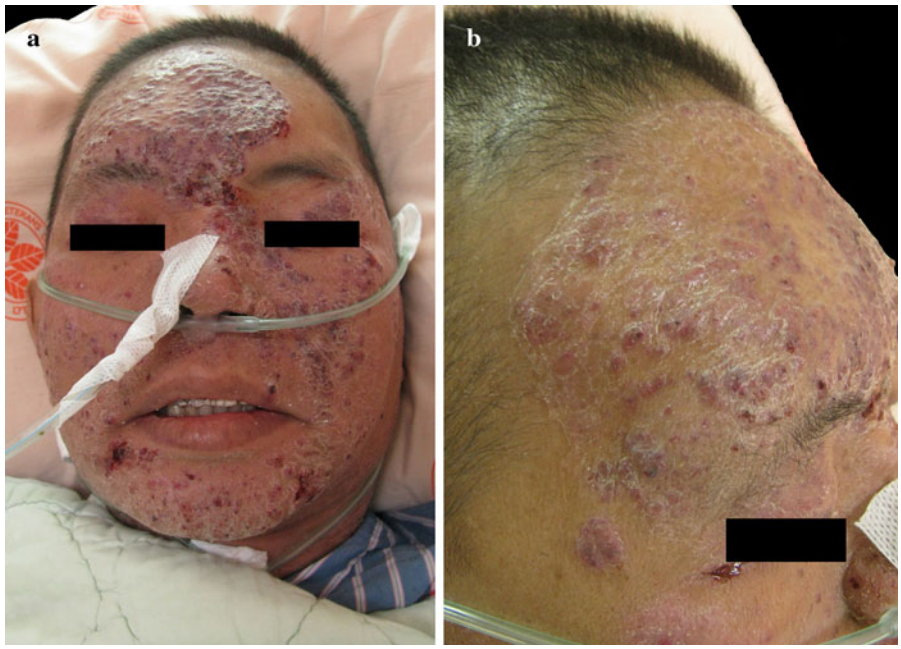

Fig. 1 Large dusky-red verrucous papuloplaques and nodules were scattered along the forehead, as well as in the periorbital area and on the cheeks, mandible, and neck. The lesions had a relatively well-defined border and were covered in white scales and hemorrhagic crusts. **a** front view, **b** lateral close-up view

free of skin tinea, making the source of fungus from skin surface less likely. Thus, the final diagnosis was extensive deep dermatophytosis with possible hematogenous dissemination caused by *T. rubrum*.

Discussion

Rarely, *T. rubrum* can cause aggressive and invasive infection at immunocompromised populations [4–8]. The three major deep invasive form of dermatophytosis are Majocchi's granuloma, deep dermatophytosis, and disseminated dermatophytosis. Majocchi's granuloma, also called nodular granulomatous perifolliculitis, described by Professor Domenico Majocchi at 1883 [7, 9], is an infection of dermal and subcutaneous fat. This is associated with disruption of hair follicles and spreading of fungi into dermis and subcutis, which produces a granulomatous reaction. Both normal population and immunosuppressed patient may be affected by this type of infection [2, 7, 9, 10]. In immunocompromised hosts, *T. rubrum* infection may also present as extensive, deep, or invasive dermatophytosis mainly at extremities, and there is only subcutaneous involvement without involvement of internal organs [2, 4, 6, 7, 11–13].

In the extensive review of invasive dermatophytosis by Marconi et al. [14], they made the conclusion that depressed immune function, atopy, and lymphoproliferative disorders are important predisposing factors of dissemination. *T. rubrum* and *Trichophyton violaceum* are two most common pathogens. Other species included *Trichophyton verrucosum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *and Microsporum audouinii* [14]. Our report added another case of extensive deep dermatophytosis caused by *T. rubrum*.

Dermatophytes usually infect the stratum corneum only and will not actively penetrate the cellular layer of the epidermis. However, they can be introduced into the deep tissue by minor trauma such as scratching. Follicular invasion is another portal of entry. Disruption of infected follicles and spreading of the fungal elements into dermis can result in Majocchi's granuloma and dermatophytic pseudomycetoma. Once survived in the host dermis, the fungi will grow restrictively under the control by the host's immune defense, or rarely, grow profoundly if the host's

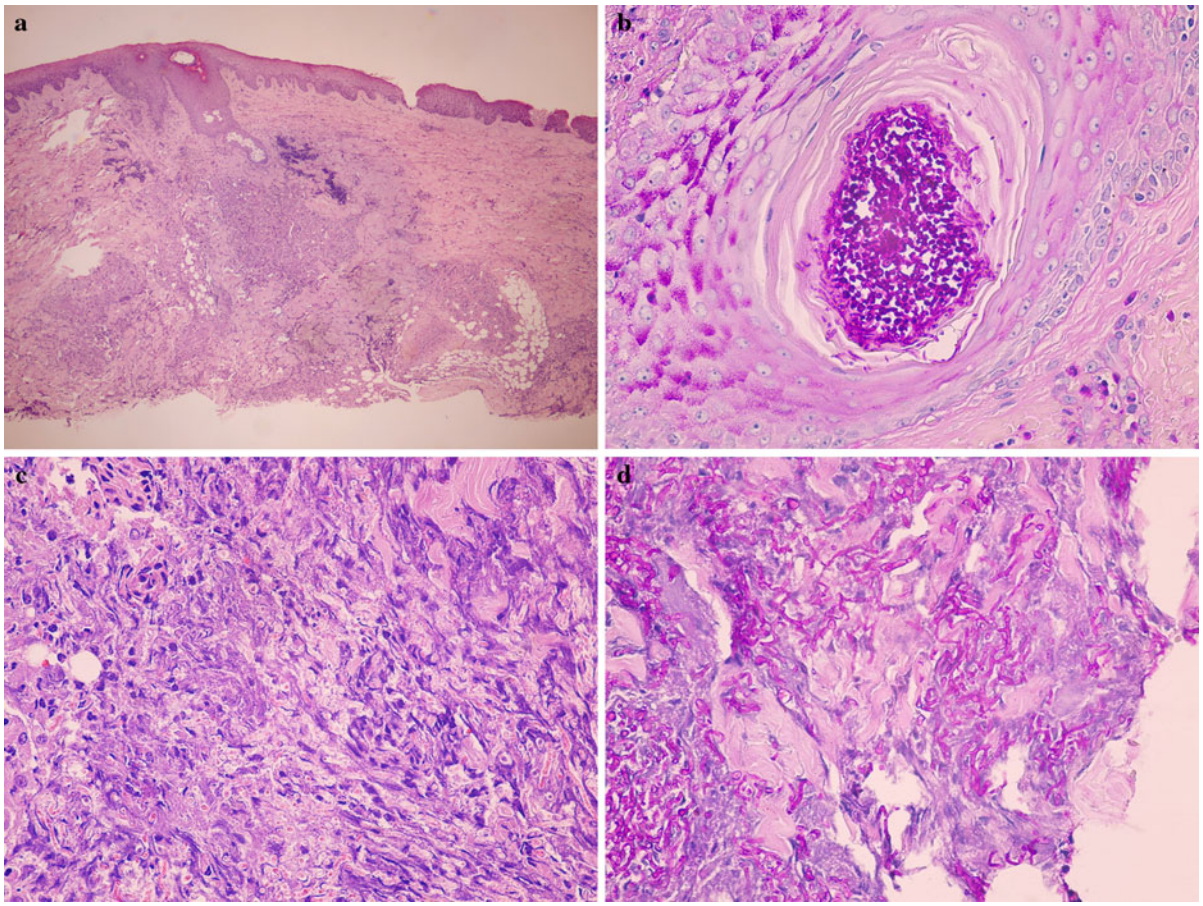

Fig. 2 **a** On histopathologic examination, there was dermal and periadnexal mixed inflammatory cell granulomatous inflammation, as well as several crushed and necrotic areas, under low-power view. (H&E stain, ×40). **b** The hair follicles were dilated and filled with round fungal spores and septate hyphae (periodic acid-Schiff stain, ×100). Dense branching fungal hyphae with large round chlamydospores infiltrated the dermis under stains of (**c**) H&E (×100) and (**d**) PAS (×100)

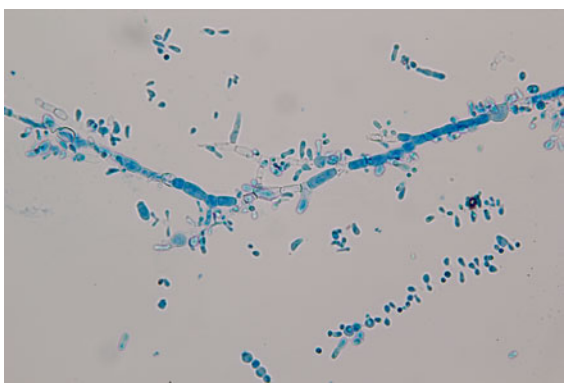

Fig. 3 The slide culture of the fungus under microscope showed microconidia of variable sizes arranged alongside the hyphae. A few intercalary chlamydospores were also observed

immune function is suppressed. Hematogenous and lymphatic spreading may ensue and result in disseminations. Although there is only evidence from animal experiments, the report by Marconi et al. [14] demonstrating angioinvasion of dermatophyte in histopathology supported this view of point [15]. According to the clinical presentations, mycology and histopathology evidence of our case, the spreading and possible hematogenous dissemination in our case should be resulted from the infection of hair follicles and predisposed by host's immune deficiency.

Liver cirrhosis has been regarded as an important risk factor for disseminated fungal infection such as cryptococcosis, mucormycosis, aspergillosis, and candidiasis [14–22]. In these infections, skin, lymph

nodes, nasal sinuses, orbit, peritoneum, lung, and central nervous systems might be involved. The mortality is generally high in this patient group. Among all reported cases of deep dermatophytosis, only one concerned a patient with liver cirrhosis [14], as it occurred in the present case. Although whether the fatal outcomes result directly from dermatophyte infection or not is unknown, the clinicians should know about this comorbidity.

Currently, there is no consensus on the treatment for disseminated and invasive dermatophytosis. Terbinafine, itraconazole, ketoconazole, amphotericin, fluconazole, and griseofulvin have been used as monotherapy or in combinations. The treatment efficacy is equivocal and case dependent. In general, the failure rate of disseminated dermatophytosis is higher than that of deep ones [15]. Further studies to evaluate the efficacy of antifungal therapy are needed in setting up the guideline for treating invasive dermatophytosis.

There are two points worth of notice in our case. First, the histopathology of our case is striking. The fungal load in the dermis is so high that can be seen even just by the H&E staining. This may result from severe immunosuppressed status of the patient, and the immune system cannot inhibit the proliferation of the fungus. Second, the fungal isolate has some variable-sized microconidia alongside of the hyphae and chlamydospores on hyphae, which makes the differentiation between *T. tonsurans* and *T. rubrum* difficult by morphology. The sequencing of ITS regions of rDNA, however, helps in making the identification. When morphologic and physiology characters of the dermatophyte isolate are doubtful, molecular method provides a reliable way to make a diagnosis. This case also addresses the need for a rapid identification of the fungal pathogen. Clinicians always need a timely identification of pathogen to choose proper antifungals for the treatment. This need, however, is sometimes hampered by the slow growth of the fungus or difficulty in identification. If PCR and sequencing services are available in the institute, it may shorten the time from the bench to the bedside.

In conclusion, we report a case of extensive deep dermatophytosis with possible hematogenous dissemination caused by *T. rubrum* in a patient with liver cirrhosis and chronic renal failure. Although dermatophytes usually cause superficial infections, it can behave aggressively and results in mortality especially when host immunity is compromised. Clinicians should keep a high alert to such an uncommon form of dermatophyte infection.

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