

Beyond the Superficial: Disseminated *Trichophyton rubrum* Infection in a Kidney Transplant Recipient

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Superficial dermatophyte infections are common in the general population and are readily treated with topical antifungals. Deeper invasion is rare, and dissemination to visceral organs is extremely uncommon. We describe a 66-year-old renal transplant recipient who developed disseminated *Trichophyton rubrum* infection while undergoing treatment for acute humoral rejection. The infection presented as a facial rash with subsequent dissemination to the lungs and chest wall. All sites of infection improved with combination administration of oral posaconazole and terbinafine. In this work, we review the available literature regarding management of disseminated *Trichophyton* infection and discuss therapeutic interventions for disseminated dermatophytosis in immunosuppressed hosts.

Keywords. disseminated dermatophytosis; literature review; trichophyton; transplant.

CASE REPORT

A 66-year-old male with a medical history of end-stage renal disease as a complication of hypertension and type II diabetes mellitus and preemptive deceased donor renal transplant 2 months prior presented to our hospital in October 2018 for management of recurrent surgical site infection.

Due to low-level donor-specific antibodies at the time of transplant, he received 4 doses of antithymocyte globulin (ATG), mycophenolate mofetil, pulse dose steroids, and tacrolimus. His post-transplant infection prophylaxis included single-strength trimethoprim-sulfamethoxazole, valganciclovir, and nystatin swish and swallow. In September 2018, he was admitted for a surgical site infection requiring incision, drainage, and intravenous (IV) vancomycin. Labs at the time were notable for a creatinine of 1.2 mg/dL (estimated glomerular filtration rate based on the MDRD equation, 64 mL/min/1.73 m²). Urinalysis demonstrated worsening proteinuria. This prompted a transplant kidney biopsy that revealed probable humoral rejection. Treatment was initiated with pulse-dose methylprednisolone followed by an oral prednisone taper, 5 sessions of therapeutic plasma exchange with intravenous immunoglobulin (IVIG), and continuation of his tacrolimus and mycophenolate mofetil.

He completed a 3.5-week course of intravenous vancomycin followed by daptomycin, with resolution of the erythema and collection. In October 2018, the patient reported symptoms of recurrent erythema and warmth over the kidney transplant site concerning for recurrent infection. He was readmitted and incidentally noted to have a nonpruritic, nonpainful nodular erythematous facial rash with an annular border and several necrotic papules under his left eye. The rash had developed slowly over the 2 months after transplant. Given concern for dermatophytosis, he underwent a punch biopsy of the left cheek rash. While awaiting the results of the skin biopsy, he was placed on twice-daily topical ketoconazole 2%. He was discharged with planned outpatient dermatology and infectious diseases follow-up. Of note, further history revealed that the patient's wife had been recently diagnosed with tinea corporis.

On skin biopsy (Figure 1), pathologic examination showed pseudoepitheliomatous hyperplasia with intradermal neutrophilic microabscesses, dermal acute and chronic inflammation with plasma cells, and both epidermal and dermal fungal hyphal and yeast forms. Routine bacterial culture demonstrated coagulase-negative *Staphylococcus*. KOH stain demonstrated fungal elements with septate hyphae. Fungal culture was negative, and acid-fast stain and culture were negative. Tissue was sent for fungal 18S PCR (University of Washington, Seattle, WA, USA) and revealed *Trichophyton rubrum complex* DNA.

After 3 weeks of topical treatment, he returned with several new indurated, violaceous plaques extending to the left malar cheek and jaw line and a new nodule on his left chest wall (Figure 2). A biopsy of the chest wall lesion was performed. Staging for disseminated infection included a computed tomography (CT) scan of the chest, which revealed a large solid cluster of nodules in the left upper lobe of the lung surrounded by ground-glass opacities

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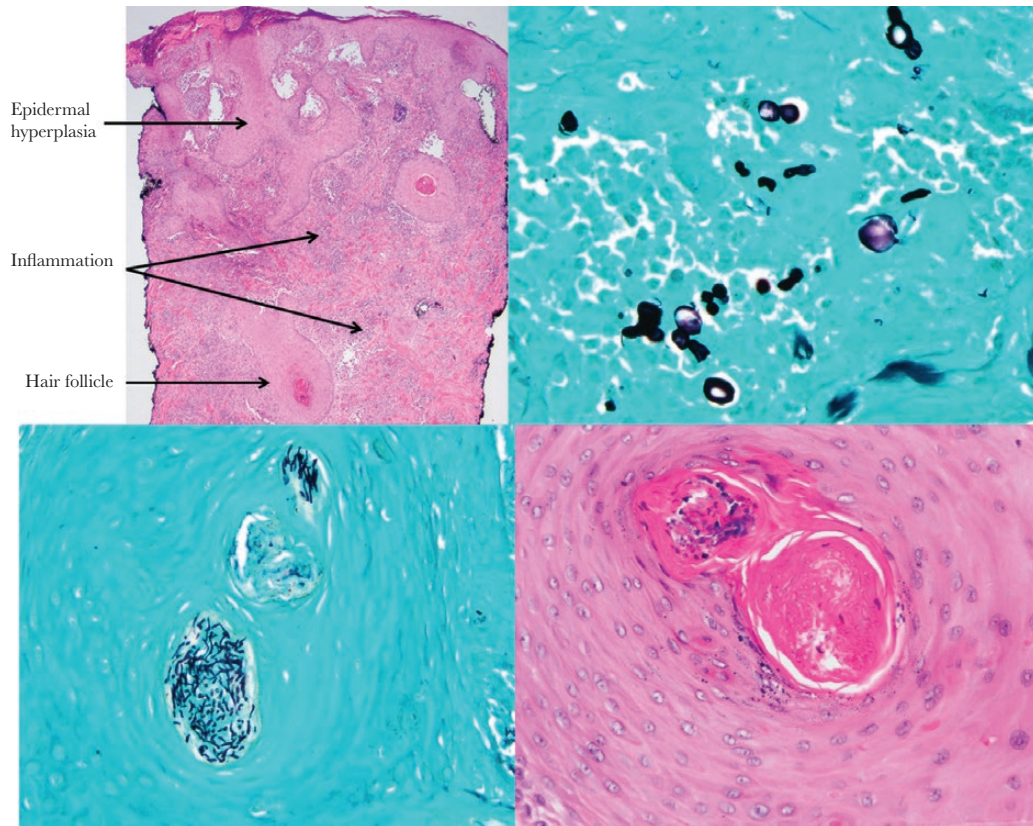


Figure 1. Skin punch biopsy showing: marked epidermal and follicular hyperplasia and marked dermal inflammation (top left), irregular shapes of invasive dermatophyte fungal forms in deep dermis (top right), an opening of a hair follicle with typical dermatophyte fungal forms (grocott methenamine silver stain bottom left, and hematoxylin and eosin stain bottom right).

concerning for a disseminated fungal process (Figure 3). Routine bacterial blood cultures and mycologic blood cultures (Bactec Myco/F Lytic culture, BD, Franklin Parks, NJ, USA) were negative. Serum (1,3)- β -D-glucan (Fungitell assay; Associates of Cape Cod, Inc., East Falmouth, MA, USA) was elevated at >500 pg/mL. Transbronchial and transthoracic sampling of the lung nodules was considered. However, this was deemed too high risk given the proximity of the nodules to the fissure.

The chest wall biopsy revealed fungal hyphae within the follicular contents and numerous pan-dermal irregularly shaped fungal hyphae and yeast-like forms, consistent with cutaneous fungal infection with features suggestive of deep dermatophytosis. Pathology demonstrated associated pseudoepitheliomatous hyperplasia, intraepidermal and dermal mixed neutrophilic, lymphohistiocytic, and eosinophilic inflammation with a foci of neutrophilic



Figure 2. Facial lesion and chest lesion on second presentation (far left, center) and facial lesion after 3 weeks of systemic antifungal therapy.

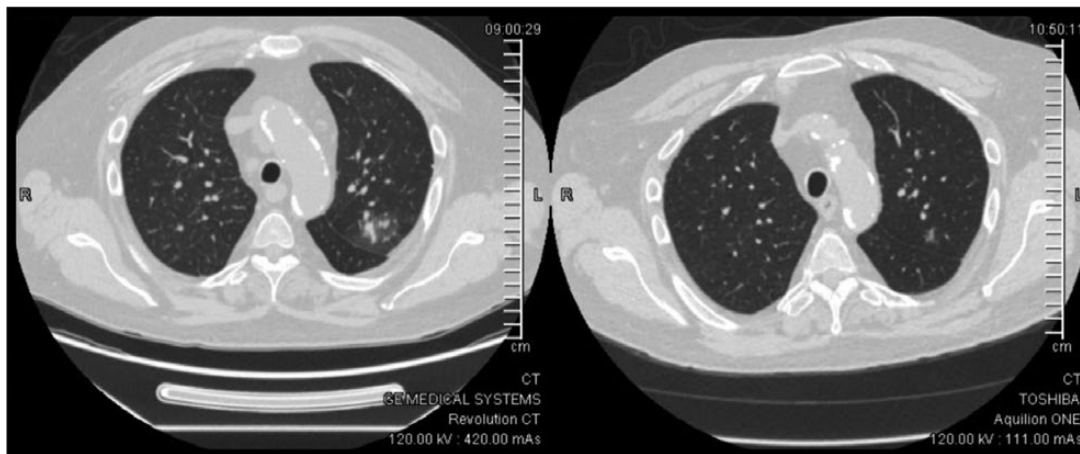


Figure 3. Chest computed tomography scan on presentation (left) and after 2 weeks of systemic antifungal therapy.

abscess formation. KOH stain demonstrated fungal elements with septate hyphae. Fungal culture revealed *Trichophyton rubrum*. Fungal confirmation and susceptibility testing were subsequently obtained through phenotypic characterization and DNA sequencing at University of Texas Health Science Center Health (San Antonio, TX, USA) (Supplementary Table 1), although they were not available at the time of initiation of antifungal therapy.

Based on the results of his chest imaging and skin biopsy findings, a presumptive diagnosis of disseminated dermatophytosis with *Trichophyton rubrum* was made. He was initiated on voriconazole (loading dose of 6 mg/kg dose \times 2 doses, followed by maintenance dose of 4 mg/kg q12 hours) and terbinafine (500 mg PO q12 hours). Multiple concomitant medications (including his tacrolimus) required adjustment due to drug–drug interactions. In light of the recent rejection episode, there was no reduction in his immunosuppressive regimen.

One week into his antifungal therapy, the patient noted visual hallucinations (voriconazole trough, 5.4 mcg/mL) suspected to be related to the voriconazole therapy. Voriconazole was switched to posaconazole (4 mg/kg daily). Terbinafine 500 mg PO q12 hours was continued as a second antifungal agent. Repeat CT imaging 2 weeks into systemic treatment showed a decrease in size of the lung nodules with only mild ground-glass changes remaining (Figure 3).

At 3 weeks, there was resolution of the chest wall lesion and dramatic improvement in the facial lesion (Figure 2). Combination antifungal therapy was continued until January 2019 (2 months). At that time, the patient had experienced substantial clinical improvement, and the results of the antifungal susceptibility testing were available. He was consolidated into single-agent terbinafine 500 mg PO q12 hours. By February 2019, there was near complete resolution of the skin rash. Only a single faint papule remained on the left cheek. During this time, the patient developed worsening renal failure requiring

initiation of dialysis and new-onset calciphylaxis and failure to thrive. He died 6 months after his initial kidney transplant of a cardiac arrest related to underlying renal failure and cardiac dysfunction.

DISCUSSION

This case illustrates the rare syndrome of disseminated dermatophytosis from *T. rubrum* with skin and pulmonary manifestations in the setting of augmented immunosuppression for treatment of renal transplant rejection. Superficial dermatophyte infections are common in both healthy and immunocompromised patients [1, 2], including patients with HIV or after solid organ transplant [3, 4]. However, dissemination is extremely rare. Disseminated disease has been described during treatment for rejection [5, 6] and after administration of antithymocyte globulin [7, 8]. In a French case series of invasive dermatophytosis (12 solid organ transplant recipients), half the patients had an episode of rejection before developing invasive dermatophytosis [5]. *T. rubrum* was the most commonly isolated organism [2–4, 9]. *M. canis* and *T. violaceum* [2] were the organisms less frequently involved.

In the microbiology laboratory, *T. rubrum* can be identified by using a combination of morphology and microscopy techniques. Isolates are often described as having a cotton-like or wooly appearance. The yield of fungal culture can be optimized by alerting the laboratory to the possibility of dermatophyte infection. This allows for plating on appropriate media and extension of incubation time to improve the diagnostic yield. To prevent bacterial and saprophytic fungal overgrowth, chloramphenicol and cycloheximide may be added [10]. If culture techniques are not successful, PCR-based techniques may be used to identify the organism. Given reports of drug resistance and the inability to predict resistance patterns based on species-level identification, additional drug susceptibility testing is also recommended.

Superficial infections are common and are the prerequisite for any disseminated infection. This concept underlies the importance of early recognition and treatment of this disease. While Majocchi's granuloma is characterized as fungal invasion that is limited to the perifollicular area, deep dermatophytosis extends beyond that [5]. The diagnosis of invasive disease is made when there is evidence of spread beyond the deep dermis into the internal organs, as was the case with our patient. This diagnosis was further supported by his imaging findings, which demonstrated resolution in response to antifungal therapy (Figure 3).

Data to support a specific regimen for disseminated *T. rubrum* are lacking. In vitro studies have shown terbinafine, extended-spectrum azoles, and griseofulvin have activity, whereas fluconazole does not [11]. Treatment of superficial dermatophyte infections can usually be accomplished with topical agents; however, invasive disease requires systemic therapy [12, 13]. While some series have used terbinafine monotherapy [5], which is particularly efficacious in the early stages of disease, terbinafine and an azole in combination have been synergistic in vitro against some fungal species [14, 15]. Given the extent of his infection and ongoing immunosuppression, the patient was initiated on dual therapy while susceptibility data were pending. Once clinical improvement was noted and sensitivity data were known, the patient was narrowed to a single antifungal agent. However, it is important to note that there have been reports of relapse after terbinafine monotherapy [16]. Hence, patients with disseminated infections should have their treatment duration tailored to clinical response and long-term follow-up. Some patients may require treatment for months to years [16, 17]. While not possible in all patients, reduction in immunosuppression should be considered as a fundamental adjunctive measure [18].

The case illustrates a rare presentation of disseminated dermatophytosis with presumed dissemination into the lungs after treatment for renal transplant rejection. Immunocompromised patients are at risk for invasive disease. In this population, a superficial dermatophyte infection should prompt providers to carefully evaluate a patient's net state of immunosuppression, consider early treatment to prevent dissemination, and direct symptom-based imaging at sites of potential dissemination. While there are no standardized treatment guidelines for treatment of this infection, antifungal therapy may include terbinafine as a first-line agent for localized disease or combination therapy with a later-generation azole for invasive or disseminated infections. Therapy duration should be based on response to treatment, taking into consideration clinical and radiographic improvement.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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