Deep Dermatophytosis: Report of 2 Cases and Review of the Literature

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GOAL

To describe deep dermatophytosis

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Outline the epidemiology and etiology of deep dermatophytic infections.
2. Describe the clinical presentation of deep dermatophytoses.
3. Identify the dermatophytes responsible for invasive disease of the skin.

CME Test on page 468.

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Skin infections due to dermatophytes are common and generally associated with a low degree of morbidity in normal hosts. Rare cases have been reported in which the dermatophyte invaded the deep dermis, subcutis, or even internal organs. Two patients, each of whom had clinical and histological findings of a deep or locally invasive dermatophyte infection, are described. This condition typically presents as a nodular eruption that is characterized histologically by suppurative granulomatous inflammation and deposition of organisms in the reticular dermis. Recognition of the potential of dermatophytes for local invasion in susceptible hosts will help ensure proper diagnosis and timely intervention in these cases.

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Dermatophytes, by virtue of their keratinophilic properties, frequently cause fungal infections that are limited to the stratum corneum, hair, and nails. In rare instances, these fungi may invade deeper tissues or even disseminate to internal organs.[1] *Trichophyton rubrum* is the organism encountered

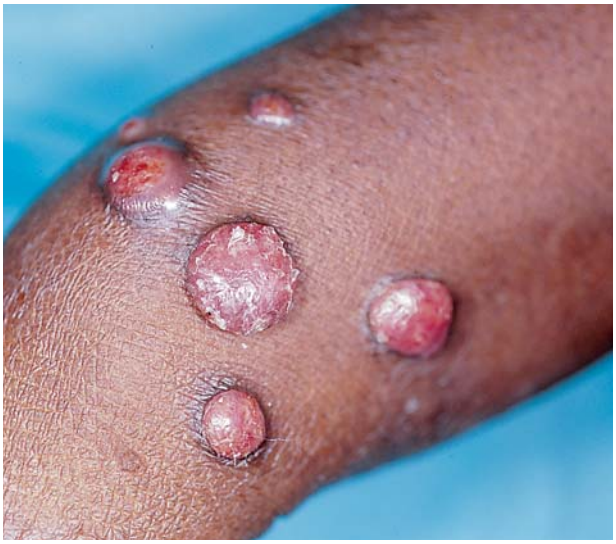

Figure 1. Slightly scaly, erythematous-to-violaceous, exophytic nodules located on the dorsal forearm of patient 1. Some of the lesions have central ulceration. Hair is very sparse on the patient's entire arm.

most commonly in fungal infections of the skin and is also the dermatophyte most often associated with the potential for tissue invasion. We describe 2 patients who presented with cutaneous nodules resulting from deep dermal invasion by *T rubrum*.

Case Reports

Patient 1—A 65-year-old black female presented with a 4-month history of pruritic, gradually enlarging lesions on her left arm. Her medical history was significant for adult-onset diabetes mellitus and hypertension, both of which had been controlled well with glyburide and methyldopa, hydrochlorothiazide. On examination of the patient's forearm, there were 6 well-demarcated, slightly scaly, erythematous-to-violaceous, firm, exophytic nodules 1 to 3 cm in diameter (Figure 1). Some of the lesions had overlying areas of ulceration. On further inspection, the nails on the patient's left first, second, third, and fifth digits were thickened and dystrophic. This problem had reportedly been chronic, but she had never sought medical evaluation. There was no associated lymphadenopathy.

Routine microscopy of one of the nodules revealed that the dermis contained closely aggregated granulomas, some of which were suppurative (Figure 2, A and B). There was a uniform distribution of pleomorphic organisms with doubly contoured walls and hyphal forms recognizable on routine sections. A periodic acid–Schiff (PAS) stain showed budding hyphal forms (Figure 3). Repeated cultures of the nodular tissue grew *T rubrum*, and a single culture of an affected nail also grew *T rubrum*.

After a diagnosis of deep dermatophyte infection was established by histopathologic findings and culture results, treatment was initiated with terbinafine, 250 mg daily. The nodular lesions began to decrease in size and induration during the first few weeks of antifungal therapy. After 12 weeks of therapy with terbinafine, the nodules regressed completely, leaving behind only tiny, hyperpigmented papules in their places.

Subsequent laboratory investigation revealed normal serum chemistries and complete blood count, except for a mild normocytic anemia. An immunodeficiency profile showed elevation of the CD8 count to 1783 cells/μL (normal 124–1099 cells/μL) and normal CD3, CD4, and CD19 counts. HIV test results were negative. Intradermal skin tests with trichophytin, mumps, *Candida*, and purified protein derivative antigens were all negative at both the 48- and 72-hour readings. A wheal-and-erythema reaction to trichophytin developed within 15 minutes of injection and then cleared spontaneously.

Patient 2—A 63-year-old white male with a history of diabetes and a cardiac transplantation presented with itchy nodules on his lower extremities of about one month's duration. He had a history of chronic tinea corporis and tinea pedis, which had been treated on an as necessary basis with topical antifungals. His other medications were tacrolimus 2 mg every morning and 1 mg every evening, mycophenolate mofetil 1250 mg twice daily, prednisone 10 mg twice daily, trimethoprim/sulfamethoxazole 160/800 mg 3 times weekly, acyclovir 400 mg 3 times a day, captopril 25 mg 3 times a day, atorvastatin 10 mg at bedtime, omeprazole 20 mg daily, amiodarone 200 mg, and insulin per sliding scale.

On the lower extremities, there were scattered, erythematous-to-violaceous, compressible nodules about 3 cm in diameter (Figure 4). The nodules were surrounded by erythematous, scaly plaques with a raised, annular border. On histologic examination of a skin biopsy, the initial sections stained with hematoxylin and eosin (H&E) showed only a mild perivascular inflammatory infiltrate with a small area of necrosis. A Gomori Methenamine Silver (GMS) stain performed on deeper sections of the tissue revealed a greater inflammatory infiltrate and fungal hyphae without involvement of follicular structures (Figure 5). A culture of the biopsied tissue revealed isolated growth of *T rubrum*.

The lesions improved significantly after starting itraconazole 200 mg twice a day, while witholding treatment with atorvastatin and omeprazole due to the possibility of drug interactions. Despite this precaution, itraconazole was discontinued after only 2 to 3 weeks of therapy because the patient had to be

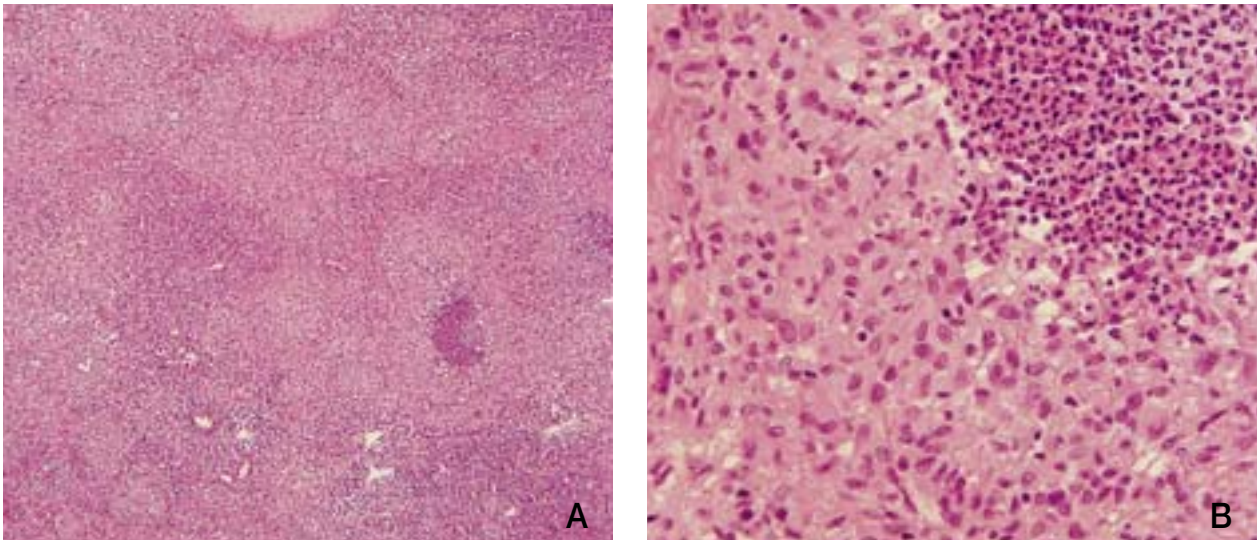

Figure 2. (A) There is a diffuse inflammatory infiltrate throughout the dermis of patient 1. The diffuse patterns are interrupted by pale micronodules composed of epithelioid histiocytes. (B) Higher magnification of an area on the lower right side showing part of a suppurative granuloma. A circumscribed defect containing closely aggregated neutrophils is outlined by palisades of epithelioid histiocytes (H&E, original magnifications ×4 and ×10, respectively).

hospitalized for cardiac decompensation of undetermined etiology. Because the lesions remained unchanged during the next several weeks, terbinafine 250 mg daily was started. After the patient completed 1 month of therapy with terbinafine, the nodular lesions had regressed almost entirely, except for some residual erythema and induration. Despite complete resolution of the adjacent annular eruption after the therapeutic course, the patient has continued to have superficial tinea infections, although the nodular lesions have not recurred.

Comment

A suppurative fungal folliculitis known as Majocchi granuloma is the most common expression of a dermatophyte infection involving the dermis.[2] With rupture of the affected follicle, follicular contents, including organisms, spill into the dermis, and a suppurative granuloma forms in the perifollicular tissue.[2-5] Majocchi granuloma occurs most frequently as nodules or plaques on the lower legs of otherwise healthy women.

Reports often indicate that dermatophytes may invade dermal or subcutaneous tissues to cause granulomatous or suppurative infections, which are clinically and histologically distinct from Majocchi granuloma. Investigators often initially attribute the eruption to a pathogen more traditionally associated with deep cutaneous or systemic infections, such as mycobacteria or nondermatophyte fungi, rather than to a dermatophyte. In contrast to fungal suppurative folliculitis or Majocchi granuloma, these deep dermatophyte infections have preferentially occurred in immunosuppressed hosts and have manifested clinically as a nodular eruption that was typically more sudden in onset, larger, or more deep-seated in location and was not necessarily associated with hair follicles.[6-9] Some authors have proposed that the absence of keratin or hair elements, the scarcity of foreign-body giant cells, the lack of follicular localization, and the presence of deep dermal or subcutis involvement on routine microscopy are suggestive of a truly invasive dermatophyte infection, rather than Majocchi granuloma.[5,8-10]

Despite careful consideration of these clinical and histological features, accurate differentiation between the 2 disease processes may be difficult. Whether or not deep or locally invasive dermatophyte infections are sufficiently unique to support their classification as a distinct entity remains to be determined. It is possible that both types of infection represent a single pathologic process, with manifestations that vary in severity from mild localized disease to severe widespread disease. Majocchi granuloma may represent the most indolent form of dermatophytosis involving the dermis, whereas the cases in this report described as deep or invasive may represent a more aggressive process because of impaired host resistance. The most severe or extreme end of this spectrum includes the rare cases of dermatophytosis that involve the bone,[1,11,12] lymph nodes and lymphatics,[8,13-15] liver,[16] spleen,[16] and even the central nervous system.[1,11,17]

In patients presenting with deep dermatophytosis, a history of chronic tinea infections can often be obtained, as in both of our cases.[4] Locally invasive dermatophytosis has been identified most commonly

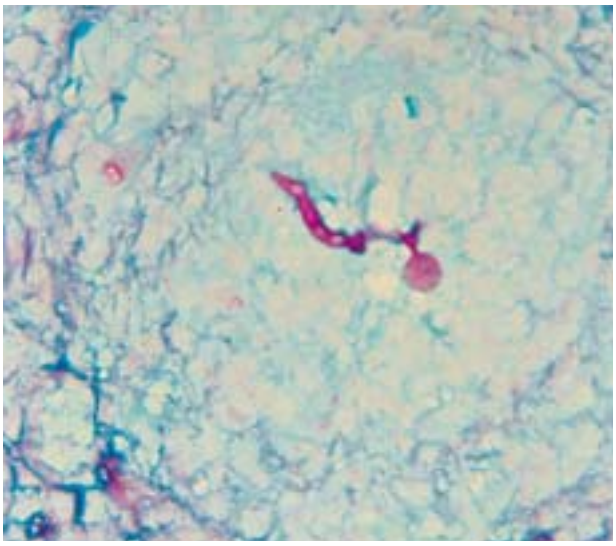

Figure 3. A branching hyphal form in the center of the granuloma of patient 1 is demonstrated by periodic acid–Schiff stain with diastase digestion and green counterstain (original magnification ×40).

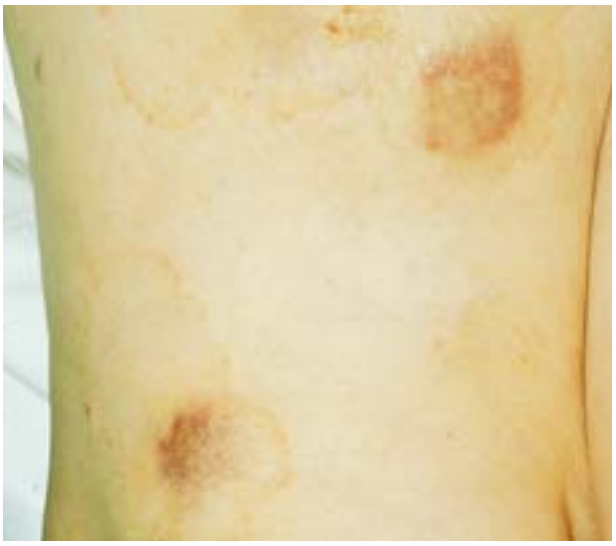

Figure 4. Large, erythematous, fluctuant nodules surrounded by annular, scaly plaques, with central clearing located on the lower extremities in patient 2.

in immunocompromised patients, especially in organ transplant recipients.[4,18,19] Other patients with deep dermatophytosis were predisposed because of immunosuppressive therapy for conditions such as idiopathic interstitial lung disease,[10] Behcet's syndrome,[20] rheumatoid arthritis,[21,22] lupus erythematosus,[23] and bullous pemphigoid.[9] Some patients with immunosuppression secondary to a neoplasm or to chemotherapy for underlying malignancy also have been reported with locally invasive dermatophyte infections.[4-6,16,24] Depressed cell-mediated immunity, either because of an independent immunologic defect, AIDS, or atopic dermatitis, has been the predisposing factor in other patients.[8,13,19,25,26] In some reported patients, no condition predisposing to immunosuppression could be found.[11,27]

The failure to elicit a delayed-type hypersensitivity reaction on intradermal skin testing in our first patient indicates the presence of defective cell-mediated immunity.[28] The lack of response to all 4 antigens suggests that her immunologic deficit is generalized and is not specific for the trichophytin antigen.[29,30] Although the patient had long-standing diabetes mellitus, no specific cause for her immunologic abnormalities was identified.

Deep cutaneous infections with a dermatophyte can present in various forms, including abscesses,[7,21,31-34] subcutaneous or exophytic nodules,[11,19,26,35] and mycetomas (or pseudomycetomas).[27,36,37] In general, lesions are dusky, hemorrhagic, erythematous to violaceous, fluctuant to firm, papules or nodules, or plaques[5,6,24,38] and may be associated with lymphadenopathy.[11] Some lesions are ulcerated or have purulent drainage.[10,24,25] Pain and tenderness of the skin lesions is common, although both of our patients complained only of pruritus.

Most patients have only a few nodules, but the lesions have ranged in number from only 1 to more than 100.[16] Although lesions are usually 1 cm to several centimeters in diameter, some have been reported as large as 10 cm.[4] They have been observed on the face, scalp, and trunk, but the most common location is on the extremities. In patients with a preexisting superficial dermatophyte infection, the invasive lesions usually develop near to the initial eruption.[4,18] The portal of entry is usually unknown, but possible causes include follicular rupture,[7,24,31] direct cutaneous invasion[5,11,24,25] (which may be augmented by potent topical steroid use or trauma), and even hematogenous seeding in selected cases.[9,16]

The dermatophyte most often responsible in cases of invasive skin disease is *T rubrum*.[4-6,9,10,16,18,22,24,25,31-33,35] Other organisms that have been reported to cause deep dermatophytosis include *Trichophyton violaceum*,[8,13-15,26,39] *Microsporum canis*,[19,23,40,41] *Microsporum ferrugineum*,[27,37] *Epidermophyton floccosum*,[20] *Trichophyton mentagrophytes*,[1,40] *Trichophyton verrucosum*,[16] *Trichophyton tonsurans*,[14,15] *Microsporum audouinii*,[17] and *Trichophyton schoenleinii*.[6] There are also scattered reports of nondermatophyte "superficial" fungi such as *Trichosporon cutaneum (beigelii)* causing locally invasive skin infections.[42,43] This organism, as well as *Malassezia furfur*, is becoming increasingly recognized as an important cause of septicemia in neonates and immunosuppressed hosts.[44,45]

Hypereosinophilia[8,26] and elevated IgE levels[1,8,16] are both frequently observed laboratory disturbances in

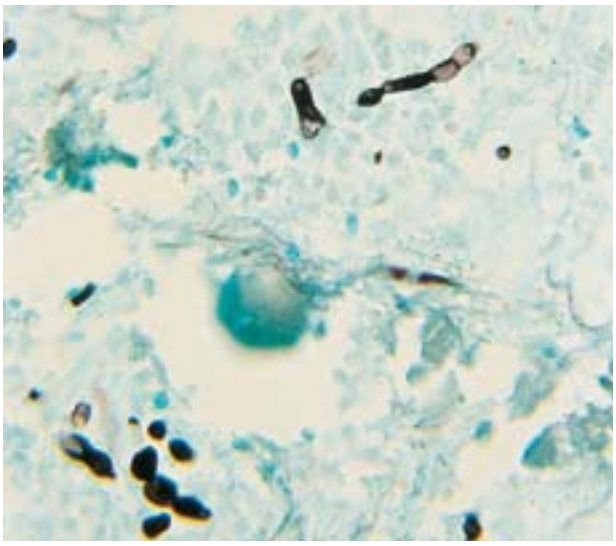

Figure 5. Fungal organisms are loosely and irregularly clustered in the granulomas of patient 2 (Gomori Methenamine Silver, original magnification ×40).

patients with invasive dermatophyte infections. Skin biopsy specimens show a granulomatous reaction and occasional necrotic areas located in the deep dermis or subcutis.[1,4,7,8,16,24,25,31] The granulomatous infiltrates may consist of giant cells, lymphocytes, plasma cells, histiocytes, and eosinophils. Suppuration is often, but not invariably, present. Septated hyphae, some of which may be swollen or have unusual morphologic characteristics, are generally found inside giant cells, as well as extracellularly in the lower dermis and subcutis. Round-to-oval sporelike structures can sometimes be visualized in the corium. Fungal organisms may or may not be found in the epidermis.[14,15,24-26,32]

Treatment with antifungal drugs is usually curative in cases of deep dermatophyte infections, as in our cases. Although griseofulvin and ketoconazole have each been used successfully for this condition,[4,5,9,20,23,24,36] terbinafine and the newer azoles, such as itraconazole and fluconazole, have been employed in recent cases with promising results.[6,11,13,25] The possibility of significant drug interactions exists particularly with itraconazole treatment, and this problem may have contributed to the cardiac decompensation in patient 2. In cases of locally invasive disease resistant to pharmacological agents, surgical excision has been performed with complete resolution of the infection.[27,42]

Both of our patients presented with an uncommon manifestation of a dermatophyte infection. These cases emphasize the wide range of clinical features of dermatophytosis and suggest that this type of infection be considered in the differential diagnosis of a patient with nodular lesions. These cases also highlight the importance of culture identification because our initial evaluation of the nodular lesions in both patients did not include *T rubrum* infection as a likely cause. Because the percentage of immunosuppressed patients in the general population is steadily increasing, deep dermatophyte infections may be encountered more frequently. Increased awareness of the locally invasive potential of dermatophytes will hopefully contribute to a proper diagnosis and generate further research into the pathogenesis of this process.

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