Extensive Multidrug-Resistant Dermatophytosis From *Trichophyton indotineae*

Toan S. Bui, BS; Jessica B. Chan, MD; Kenneth A. Katz, MD, MSc, MSCE

PRACTICE **POINTS**

- *Trichophyton indotineae* can cause extensive dermatophytosis that often is resistant to terbinafine and in some cases to other antifungals.
- Only molecular testing, which is not widely available, can distinguish *T indotineae* from other dermatophytes.
- Suspected or confirmed cases of *T indotineae* dermatophytosis should be reported to public health agencies to provide assistance with testing, as well as surveillance, prevention, and control of infection.

To the Editor:

Historically, commonly available antifungal medications have been effective for treating dermatophytosis (tinea). However, recent tinea outbreaks caused by *Trichophyton indotineae*—a dermatophyte often resistant to terbinafine and sometimes to other antifungals—have been reported in South Asia, Europe, the Middle East, Southeast Asia, and Australia.[1-5]

Three confirmed cases of *T indotineae* dermatophytosis in the United States were reported in 2023 in New York[3,6]; a fourth confirmed case was reported in 2024 in Pennsylvania.[7] Post hoc laboratory testing of fungal isolates in New York in 2022 and 2023 identified an additional 11 cases.[8] We present a case of extensive multidrug-resistant tinea caused by *T indotineae* in a man in California.

An otherwise healthy 65-year-old man who had traveled to Europe in the past 3 months presented to his primary care physician with a widespread pruritic rash (Figure 1). He was treated with 2 weeks of oral terbinafine 250 mg/d and topical medicines, including clotrimazole cream 1%, fluocinonide ointment 0.05%, and clobetasol ointment 0.05% without improvement. Subsequently, 2 weeks of oral griseofulvin microsize 500 mg/d also proved ineffective. An antibody test was negative for HIV. His hemoglobin A_{1c} was 6.2% (reference range, ≤5.6%). The patient was referred to dermatology.

Erythematous plaques—many scaly throughout and some annular with central clearing—were present on the arms, legs, and torso as well as in the groin. Honey crust was present on some plaques on the leg. A potassium hydroxide preparation showed abundant fungal hyphae. Material for fungal and bacterial cultures was collected. The patient was treated again with oral terbinafine 250 mg/d, an oral prednisone taper starting at 60 mg/d

Toan S. Bui is from the University of Maryland School of Medicine, Baltimore. Dr. Chan is from Kaiser Permanente East Bay Medical Group and Regional Dermatopathology, both in Oakland, California. Dr. Katz is from the Dermatology Department, Kaiser Permanente San Francisco Medical Center, California.

The authors report no conflict of interest.

Correspondence: Kenneth A. Katz, MD, MSc, MSCE, Dermatology Department, Kaiser Permanente San Francisco Medical Center, 1600 Owens St, 9th Floor, San Francisco, CA 94158 (kenneth.a.katz@kp.org).

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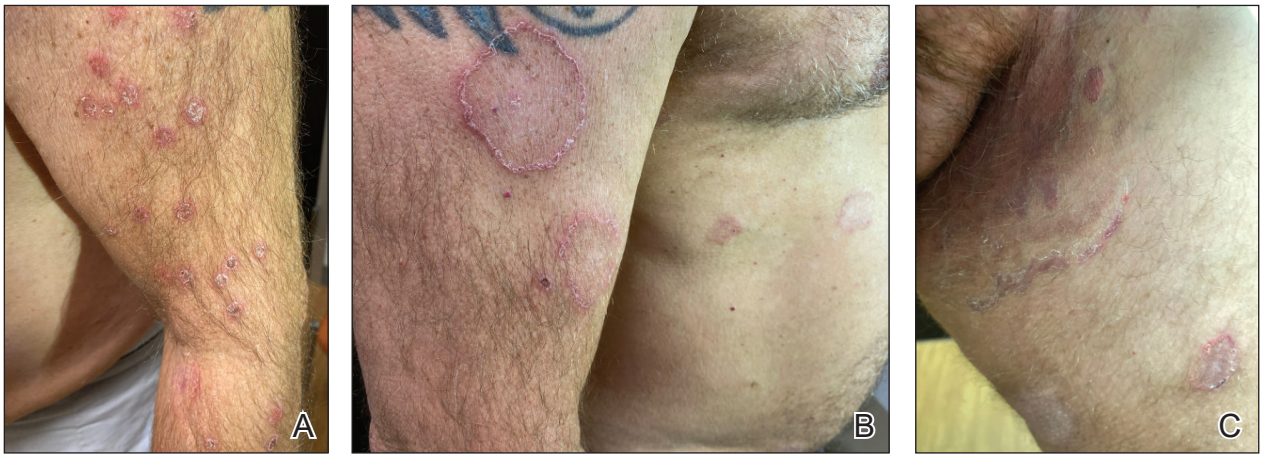

FIGURE 1. *Trichophyton indotineae* dermatophytosis. A, Multiple annular, erythematous, scaly plaques on the upper left arm. B, Two annular erythematous plaques with scaly borders on the upper right arm. C, Erythematous plaques with scaly borders on the superior medial fold of the left thigh.

for a presumed id reaction, and various oral antihistamines for pruritus; all were ineffective. A bacterial culture showed only mixed skin flora. Oral fluconazole 200 mg/d was prescribed. A skin biopsy specimen showed compact orthokeratosis and parakeratosis of the stratum corneum with few neutrophils and focal pustule formation (Figure 2). Superficial perivascular inflammation, including lymphocytes, histiocytes, and few neutrophils, was present. A periodic acid–Schiff stain showed fungal hyphae in the stratum corneum and a hair follicle (Figure 3). After approximately 2 weeks, mold was identified in the fungal culture. Approximately 2 weeks thereafter, the organism was reported as *Trichophyton* species.

The rash did not improve; resistance to terbinafine, griseofulvin, and fluconazole was suspected clinically.

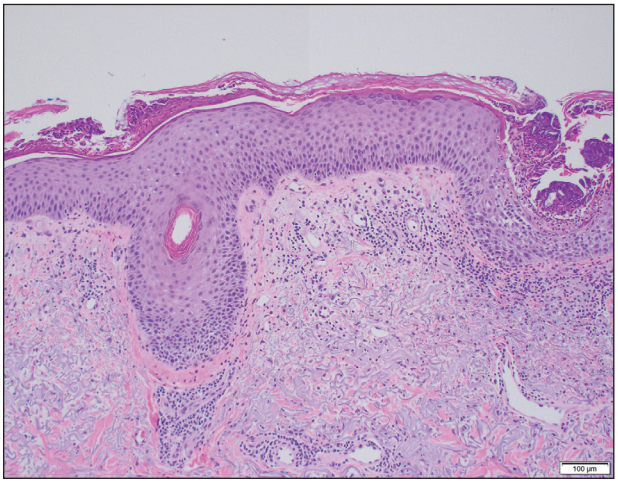

FIGURE 2. Compact orthokeratosis, parakeratosis, neutrophils, and pustules in the stratum corneum as well as lymphocytic and neutrophilic perivascular inflammation in the dermis due to *Trichophyton indotineae* dermatophytosis (H&E, original magnification ×100). Reference bar indicates 100 µm.

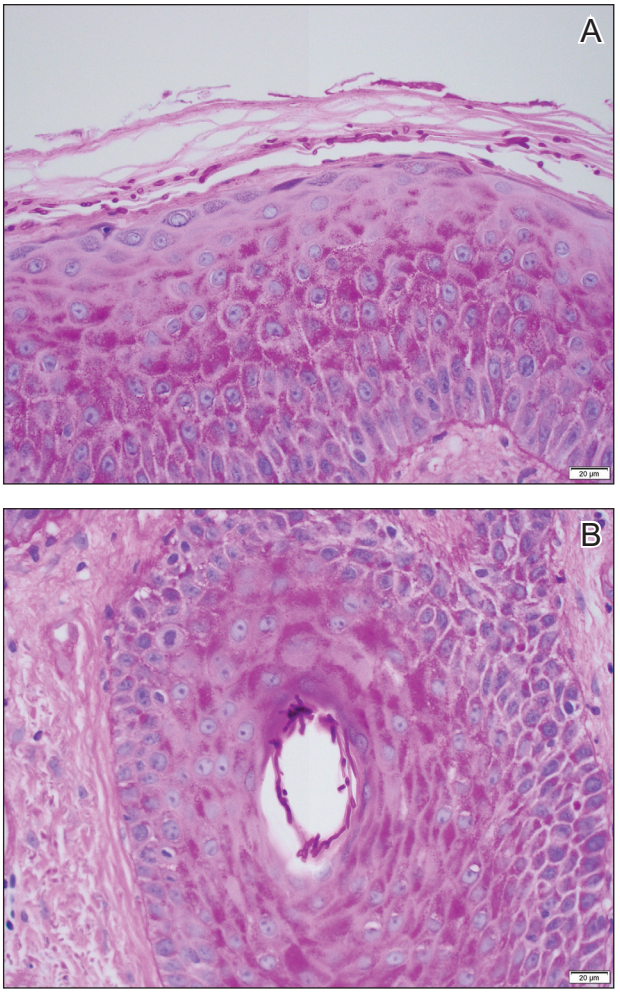

FIGURE 3. A and B, Fungal hyphae in the stratum corneum and hair follicle, respectively, due to *Trichophyton indotineae* dermatophytosis (periodic acid–Schiff, original magnifications ×400). Reference bar indicates 20 µm.

The fungal isolate was sent to a reference laboratory (University of Texas Health Science Center, San Antonio). Meanwhile, oral itraconazole 200 mg twice daily and ketoconazole cream 2% were prescribed; the rash began to improve. A serum itraconazole trough level obtained 4 days after treatment initiation was 0.5 μg/mL (reference range, ≥0.6 μg/mL). The evening itraconazole dose was increased to 300 mg; a subsequent trough level was 0.8 μg/mL.

Approximately 1 month after the fungal isolate was sent to the reference laboratory, *T indotineae* was confirmed based on polymerase chain reaction (PCR) testing of internal transcribed spacer region sequences. Minimum inhibitory concentrations (MICs) obtained through antifungal susceptibility testing (AFST) were reported for fluconazole (8 μg/mL), griseofulvin (2 μg/mL), itraconazole (≤0.03 μg/mL), posaconazole (≤0.03 μg/mL), terbinafine (≥2 μg/mL), and voriconazole (0.125 μg/mL).

Approximately 7 weeks after itraconazole and ketoconazole were started, the rash had completely resolved. Nearly 8 months later (at the time this article was written), the rash had not recurred.

We report a unique case of *T indotineae* in a patient residing in California. Post hoc laboratory testing of dermatophyte isolates sent to the University of Texas reference laboratory identified terbinafine-resistant *T indotineae* specimens from the United States and Canada dating to 2017; clinical characteristics of patients from whom those isolates were obtained were unavailable.[9]

Trichophyton indotineae dermatophytosis typically is more extensive, inflamed, and pruritic, as well as likely more contagious, than tinea caused by other dermatophytes.[5] Previously called *Trichophyton mentagrophytes* genotype VIII when first isolated in 2017, the pathogen was renamed *T indotineae* in 2020 after important genetic differences were discovered between it and other *T mentagrophytes* species.[5] The emergence of *T indotineae* has been attributed to concomitant use of topical steroids and antifungals,[5,10] inappropriate prescribing of antifungals,[5] and nonadherence to antifungal treatment.[5]

Likely risk factors for *T indotineae* infection include suboptimal hygiene, overcrowded conditions, hot and humid environments, and tight-fitting synthetic clothing.[4] Transmission from family members appears common,[5] especially when fomites are shared.[4] A case reported in Pennsylvania likely was acquired through sexual contact.[7] Travel to South Asia has been associated with acquisition of *T indotineae* infection,[3,5-7] though our patient and some others had not traveled there.[3,8] It is not clear whether immunosuppression and diabetes mellitus are associated with *T indotineae* infection.[4,5,8] *Trichophyton indotineae* also can affect animals,[11] though zoonotic transmission has not been reported.[4]

Not all *T indotineae* isolates are resistant to one or more antifungals; furthermore, antifungal resistance in other dermatophyte species has been reported.[5] Terbinafine resistance in *T indotineae* is conferred by mutations in the gene encoding squalene epoxidase, which helps synthesize ergosterol—a component of the cell membrane in fungi.[2,4,5,12] Although clinical cut-points for MIC obtained by AFST are not well established, *T indotineae* MICs for terbinafine of 0.5 μg/mL or more correlate with resistance.[9] Resistance to azoles has been linked to overexpression of transporter genes, which increase azole efflux from cells, as well as to mutations in the gene encoding lanosterol 14α demethylase.[4,12,13]

Potassium hydroxide preparations and fungal cultures cannot differentiate *T indotineae* from other dermatophytes that typically cause tinea.[5,14] Histopathologic findings in our case were no different than those of non–*T indotineae* dermatophytes. Only molecular testing using PCR assays to sequence internal transcribed spacer genes can confirm *T indotineae* infection. However, PCR assays and AFST are not available in many US laboratories.[5] Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry has shown promise in distinguishing *T indotineae* from other dermatophytes, though its clinical use is limited and it cannot assess terbinafine sensitivity.[15,16] Clinicians in the United States who want to test specimens from cases suspicious for *T indotineae* infection should contact their local or state health department or the Centers for Disease Control and Prevention for assistance.[3,5]

Systemic treatment typically is necessary for *T indotineae* infection.[5] Combinations of oral and topical azoles have been used, as well as topical ciclopirox, amorolfine (not available in the United States), and luliconazole.[1,5,17-21]

Itraconazole has emerged as the treatment of choice for *T indotineae* tinea, typically at 200 mg/d and often for courses of more than 3 months.[5] Testing for serum itraconazole trough levels, as done for our patient, typically is not recommended. Clinicians should counsel patients to take itraconazole with high-fat foods and an acidic beverage to increase bioavailability.[5] Potential adverse effects of itraconazole include heart failure and numerous drug-drug interactions.[5,22] Patients with *T indotineae* dermatophytosis should avoid sharing personal belongings and having skin-to-skin contact of affected areas with others.[4]

Dermatologists who suspect *T indotineae* infection should work with public health agencies that can assist with testing and undertake infection surveillance, prevention, and control.[5,23] Challenges to diagnosing and managing *T indotineae* infection include lack of awareness among dermatology providers, the need for specialized laboratory testing to confirm infection, lack of established clinical cut-points for MICs from AFST, the need for longer duration of treatment vs what is needed for typical tinea, and potential challenges with insurance coverage for testing and treatment. Empiric treatment with itraconazole should be considered when terbinafine-resistant dermatophytosis is suspected or when terbinafine-resistant *T indotineae* infection is confirmed.

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