JAMA Dermatology Clinicopathological Challenge

Indurated Plaque With Ulceration on the Dorsum of the Left Hand

Juanjuan Li, MS; Xiaomo Wu, PhD; Borui Chen, MD, PhD

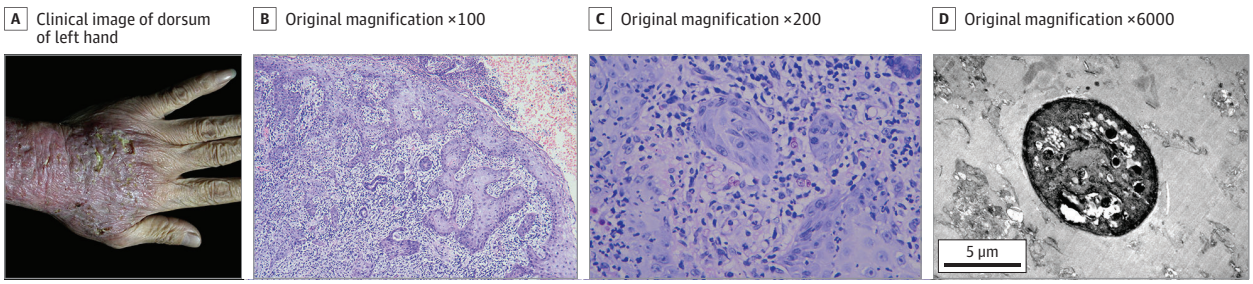

Figure. A, A large, firm, mildly swollen erythematous plaque with purulent discharge and crusting on the back of the left forearm. B, Hyperkeratosis, pseudoepitheliomatous hyperplasia, and lymphohistiocytic infiltrate with neutrophils, plasma cells, and a small amount of multinucleated giant cells in the dermis (hematoxylin-eosin). C, Periodic acid-Schiff staining. D, Transmission electron microscopy.

A man in his 70s presented with a 6-month history of a rash on the left forearm, which gradually increased in severity. The patient developed a rash on the dorsal aspect of his hand half a year ago without any pain or itching discomfort and denied any history of injury or exposure to suspected pathogens prior to onset. After self-medication with topical herbal medicine, the lesions gradually spread to the forearm and fused into plaques, and ulcers often recurred on the surface. He denied any systemic symptoms and concerns. Physical examination revealed large, firm, mildly swollen erythematous plaques on the back of the left forearm with purulent discharge and crusting (**Figure**, A). Results of routine laboratory investigations, including complete blood cell count, biochemical profile, and chest radiography, were normal. A biopsy specimen was taken for pathological examination (Figure, B-D).

WHAT IS YOUR DIAGNOSIS?

A. Chromoblastomycosis

B. Cutaneous cryptococcosis

C. Cutaneous protothecosis

D. Cutaneous leishmaniasis

Quiz at jamacmelookup.com

Diagnosis

C. Cutaneous protothecosis

Microscopic Findings and Clinical Course

Hyperkeratosis, pseudoepitheliomatous hyperplasia, and a lymphohistiocytic infiltrate with granuloma formation, neutrophils, plasma cells, and multinucleated giant cells in the dermis were observed in the pathological examination (Figure, B). Periodic acid–Schiff staining showed mulberrylike thick-walled spherical or ovoid spores of various sizes and high-density cell walls (Figure, C). Multiple endospores were highlighted by transmission electron microscopy and were irregular asexually separated schizonts (Figure, D). After identification of *Prototheco*sis *wickerhamii* by molecular sequencing technology, the diagnosis of protothecosis was confirmed. One month after oral administration of itraconazole, 0.2 g, every day, the patient's rash subsided considerably.

Discussion

Protothecosis is an emerging environmental algal disease in humans caused by the genus *Prototheca*, which are unicellular achlorophyllous saprophytic algae. Under the microscope, *Prototheca* appears as spherical or elliptical sporangia with a length of 3 to 30 µm, containing numerous endospores that can release spores through the cleavage of the sporangium wall without the presence of hyphae and blastospore structures. In 1964, Davies et al first reported a case of human cutaneous protothecosis caused by *Prototheca zopfii*.[1] Since then, there have been reports of protothecosis all over the world, but the actual incidence may be higher owing to the lack of a certain understanding of the disease.

Human infections are primarily caused by *P wickerhamii*, which is an opportunistic pathogen that is environmentally ubiquitous and can be isolated from tap water, sewage disposal systems, swimming pools, soil, human feces, and food. In humans, *Prototheca* mostly causes cutaneous infections or olecranon bursitis with repeated traumatic inoculation. After an incubation period, granuloma formation gradually occurs. Skin infections usually occur on exposed parts such as the extremities, forehead, and cheeks, and manifest as tenderness, swelling, erythematous plaques, papules, or nodules.[2] Systemic infections are usually seen in immunocompromised patients and patients with diabetes, chronic kidney failure, long-term use of steroids, AIDS, or malignant tumors,[3] where *Prototheca* can disseminate to viscera, causing life-threatening sepsis.

The differential diagnosis of protothecosis includes chromoblastomycosis, cutaneous cryptococcosis, and cutaneous leishmaniasis. Chromoblastomycosis is a chronic fungal infection of the skin and the subcutaneous tissue caused by traumatic inoculation of dematiaceous fungi with high prevalence in tropical or subtropical areas of the world.[4] Histopathologically, typical polyhedral, dark, thick-walled sclerotic bodies, 5 to 12 µm in diameter, may be observed, indicating the presence of dematiaceous fungus.[5] In systemic cryptococcosis, cutaneous lesions occur in 15% of those diagnosed and may be the first indicator of infection. *Cryptococcus* infection occurs primarily from the inhalation of infectious yeast from contaminated soil, and the presentation of primary cutaneous cryptococcosis can be quite unspecific, including acneiform lesions, purpura, vesicles, nodules, abscesses, ulcers, granulomas, pustules, draining sinuses, and cellulitis.[6] Nonetheless, encapsulated fungal pathogen in the tissue can be readily identified with routine hematoxylin-eosin staining because it is surrounded by a wide, refractile polysaccharide capsule. Leishmaniasis is caused by infection with *Leishmania* parasites that spread by the bite of phlebotomine sand flies, most frequently occurring in the tropics and subtropics of Africa, Asia, the Americas, and southern Europe.[7,8] Cutaneous leishmaniasis is the most common form of leishmaniasis, caused by more than 15 different species of the protozoan parasite *Leishmania*, transmitted by infected female sandflies.[8] The clinical presentation of cutaneous leishmaniasis depends on factors associated with the virulence of the parasite and varied individual immune response, but the most common presentations are crusted, ulcerated nodules and plaques. The lesions can persist for months, sometimes even years, leaving unpleasant-looking scars.[7] Under the light-microscopic examination after Giemsa stain (pH, 7.2), there are Leishman-Donovan bodies with rod-shaped kinetoplasts that are multiple Leishmania amastigotes 2 to 5 µm in length and 1 to 2 µm in width that can help clarify the diagnosis. Several different polymerase chain reaction tests are available for the detection of the pathogenic infection and play a critical role in differential disease diagnosis.

At present, there is no unified standard for the treatment of cutaneous protothecosis. Clinicians rely primarily on experience for treatment, and the effects are uncertain, producing varied therapeutic efficacy in different cases. The suggestion of most scholars is to use amphotericin B as the first-line drug, though others apply various antifungal drugs (eg, ketoconazole, fluconazole) or the combined use of amphotericin B and tetracycline.[2,9,10] In the present case, after 1 month of treatment with itraconazole, the patient experienced a substantial improvement.

ARTICLE INFORMATION

Author Affiliations: Dermatology Institute of Fuzhou, Dermatology Hospital of Fuzhou, Fuzhou, China (Li, Wu, Chen); Department of Biomedicine, University of Basel, Basel, Switzerland (Wu); Research Center for Medical Mycology, Department of Dermatology, Peking University First Hospital, Peking University, Beijing, China (Chen).

Corresponding Author: Borui Chen, MD, PhD, Dermatology Institute of Fuzhou, Dermatology Hospital of Fuzhou, Xihong Rd 243, Fuzhou 350025, China (pekking@gmail.com).

Published Online: November 9, 2022. doi:10.1001/jamadermatol.2022.4889

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the patient for granting permission to publish this information. We also thank Jun Chen, MD, Liqiang Weng, MD, and Qinqin Long, MD, all from the Dermatology Hospital of Fuzhou, for their assistance in pathology; Wanding Lu, MD, from the Dermatology Hospital of Fuzhou, for assisting in professional guidance and comments on this case; and Xi Lin, MS, from the Public Technology Service Center of Fujian Medical University, for support in transmission electron microscopy. They were not compensated for their contributions.

Self-assessment Credit: This article is eligible for journal-based self-assessment (1 credit) for Maintenance of Certification (MOC) from the American Board of Dermatology (ABD). After completion of an activity, please log on to the ABD website at www.abderm.org to register your credits. This may be done after each exercise or after accumulating many credits.

REFERENCES

1. Davies RR, Spencer H, Wakelin PO. A case of human protothecosis. *Trans R Soc Trop Med Hyg*. 1964;58(5):448-451. doi:10.1016/0035-9203(64)90094-X

2. Okuyama Y, Hamaguchi T, Teramoto T, Takiuchi I. A human case of protothecosis successfully treated with itraconazole. *Nihon Ishinkin Gakkai Zasshi*. 2001;42(3):143-147. doi:10.3314/jjmm.42.143

3. Seok JY, Lee Y, Lee H, Yi SY, Oh HE, Song JS. Human cutaneous protothecosis: report of a case and literature review. *Korean J Pathol*. 2013;47(6):575-578. doi:10.4132/KoreanJPathol.2013.47.6.575

4. Queiroz-Telles F, de Hoog S, Santos DW, et al. Chromoblastomycosis. *Clin Microbiol Rev*. 2017;30(1):233-276. doi:10.1128/CMR.00032-16

5. McGinnis MR. Chromoblastomycosis and phaeohyphomycosis: new concepts, diagnosis, and mycology. *J Am Acad Dermatol*. 1983;8(1):1-16. doi:10.1016/S0190-9622(83)70001-0

6. Noguchi H, Matsumoto T, Kimura U, Hiruma M, Kusuhara M, Ihn H. Cutaneous cryptococcosis. *Med Mycol J*. 2019;60(4):101-107. doi:10.3314/mmj.19.008

7. Sainz-Gaspar L, Rosón E, Llovo J, Vázquez-Veiga H. Photodynamic therapy in the treatment of cutaneous leishmaniasis. *Actas Dermosifiliogr (Engl Ed)*. 2019;110(3):249-251. doi:10.1016/j.ad.2018.02.018

8. Von Stebut E. Leishmaniasis. *J Dtsch Dermatol Ges*. 2015;13(3):191-200. doi:10.1111/ddg.12595

9. Bakuła Z, Siedlecki P, Gromadka R, et al. A first insight into the genome of *Prototheca wickerhamii*, a major causative agent of human protothecosis. *BMC Genomics*. 2021;22(1):168. doi:10.1186/s12864-021-07491-8

10. Lass-Flörl C, Mayr A. Human protothecosis. *Clin Microbiol Rev*. 2007;20(2):230-242. doi:10.1128/CMR.00032-06