Generalized *Cryptococcus albidus* in an Immunosuppressed Patient With Palmopustular Psoriasis

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Cryptococcal infection is relatively uncommon, except among immunocompromised individuals. The most common human pathogenic species is Cryptococcus neoformans. *Virtually all organs can be affected, particularly the central nervous and pulmonary systems. The prototypical manifestations of cutaneous cryptococcal infection include generalized papules, periorificial acneiform pustules, and molluscumlike vesicles on the upper body. We describe an unusual case of* Cryptococcus albidus *infection presenting atypically with generalized hemorrhagic plaques. Furthermore, we review the literature on diagnostic evaluation and treatment.*

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Case Report

An 83-year-old man presented to our dermatology clinic with a history of palmopustular psoriasis of 14 years' duration. Treatment with calcipotriene ointment 0.005%, clobetasol propionate foam 0.05%, tar, and tacrolimus ointment 0.01%, as well as systemic methotrexate, etanercept, and adalimumab, unsuccessfully controlled his debilitating disease. He markedly improved for almost 1 year with efalizumab and tacrolimus ointment 0.01%. However, 3 months prior to presentation, he developed a new eruption on his forearms that only partially responded to clotrimazole and betamethasone. He also developed a hemorrhagic crusted plaque on his scalp that was biopsied. This specimen demonstrated granulomatous dermatitis with periodic acid–Schiff, Gomori methenamine-silver, and acid-fast bacillus stains negative for fungi and bacteria. He was thought to have a mild psoriasis flare and tazarotene cream 0.05% was prescribed.

Upon follow-up to our clinic, the patient had annular, violaceous, crusted plaques on his right wrist, forearms, ears, scalp, and glabella (Figure 1). He was empirically treated with fluconazole 200 mg daily for suspected deep fungal infection. Efalizumab, tacrolimus, and tazarotene were discontinued. Bacterial culture and potassium hydroxide preparation were negative. One week later, he developed increasing erythema, hyperkeratosis, and pruritus. Two separate biopsies of his upper extremities demonstrated subcorneal pustules with a predominance of neutrophils and scattered eosinophils (Figure 2), which was suggestive of possible Sweet syndrome, drug reaction, or infection. He did not have peripheral eosinophilia. Bacterial cultures from his arm punch biopsy showed methicillin-sensitive *Staphylococcus aureus* and yeast. He was treated with dicloxacillin and his dosage of fluconazole was empirically increased to 400 mg daily.

A portion of the skin punch biopsy also was sent for fungal culture, which grew *Cryptococcus albidus*. He was admitted to the hospital for further evaluation and treatment. There was no evidence of systemic cryptococcal infection on chest radiography, head magnetic resonance imaging, and latex agglutination test for serum cryptococcal antigen. He denied any unusual environmental exposures and had no

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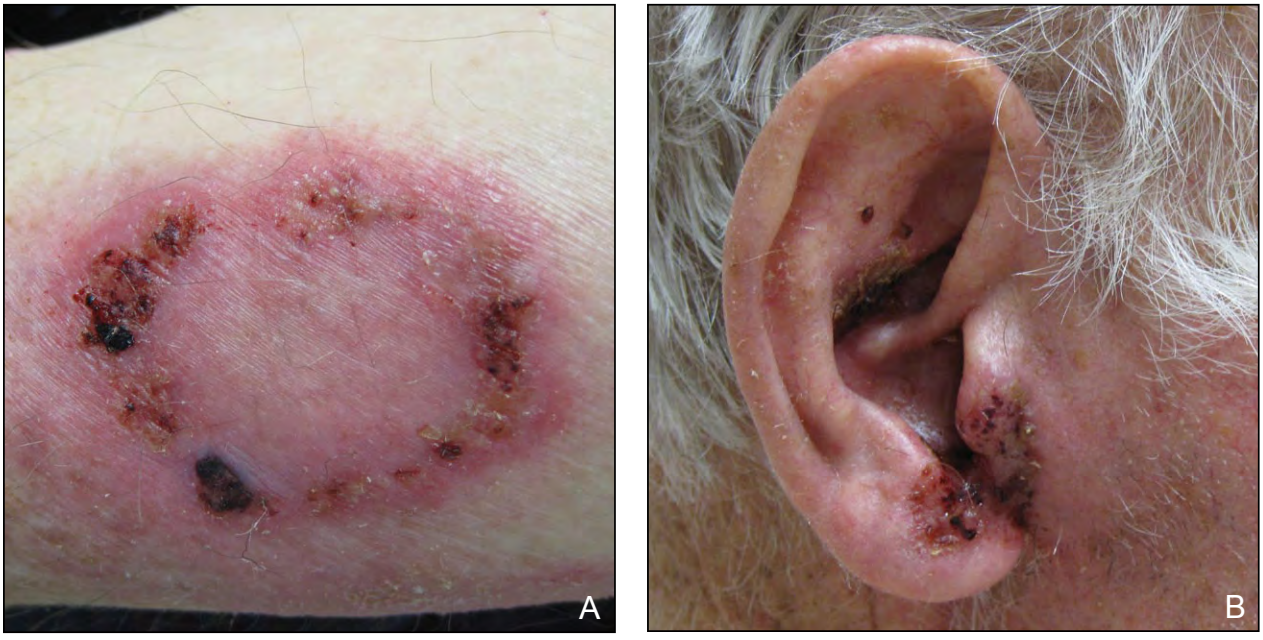

Figure 1. Annular hemorrhagic plaque with overlying crust on the forearm (A) and hemorrhagic crusts on the ear (B).

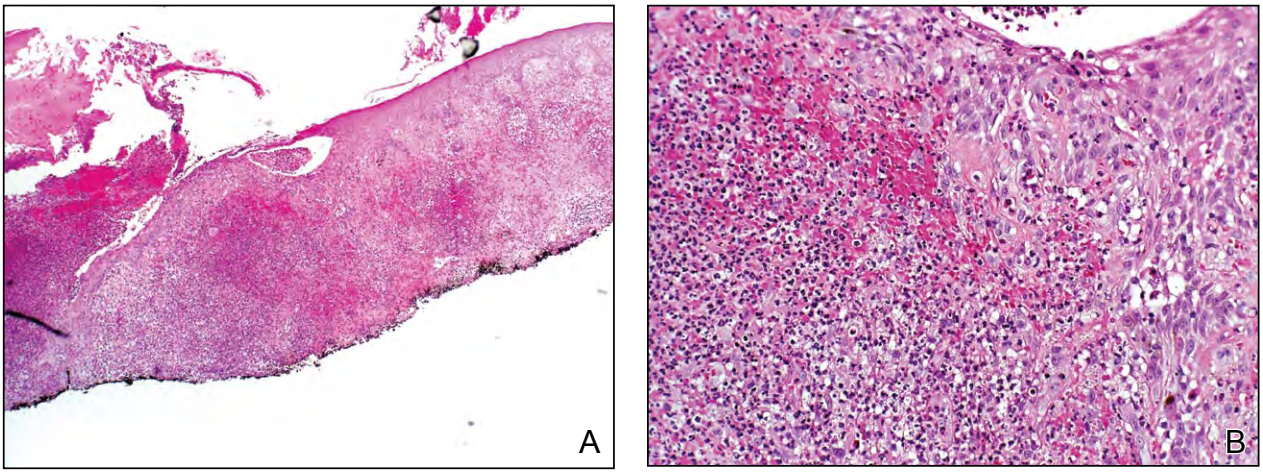

Figure 2. A skin biopsy from the upper extremity revealed a subcorneal pustule, neutrophil predominance, and scattered eosinophils (A and B)(H&E; original magnifications ×40 and ×200, respectively).

known human immunodeficiency virus risk factors. An infectious disease specialist was consulted who agreed that C *albidus* was the cutaneous pathogen rather than a mere contaminant. Lumbar puncture was not performed because the patient was taking aspirin and clopidogrel, had no overt neurologic symptoms, and had no abnormal results from head magnetic resonance imaging. The infectious disease specialist recommended continuing dicloxacillin for 2 weeks and fluconazole 400 mg daily. He developed *Acinetobacter* cellulitis of the toes, presumably via cutaneous erosions, and he was treated with acetic acid soaks and oral ciprofloxacin. The plaques resolved after 6 months of fluconazole. All treatment of palmopustular psoriasis was suspended until completion of fluconazole therapy. This event was reported to the manufacturer of efalizumab (Genentech, Inc).

Comment

Strains of *Cryptococcus*, excluding *Cryptococcus neoformans*, have been regarded as nonpathogenic and rarely cause disease.[1,2] According to a PubMed search of articles indexed for MEDLINE using the term *Cryptococcus albidus*, only 7 cases of *C albidus* cutaneous infection presented without evidence of systemic involvement.[3-9] Narayan et al[5] reported a patient with type 2 diabetes mellitus and Sézary syndrome who contracted cutaneous *C albidus* of the suprapubic abdomen and penis without evidence of systemic involvement. Unlike our case, their patient's biopsy showed numerous yeast organisms with Gomori methenamine-silver stain.[5]

The diagnosis of *C albidus* can be elusive with standard testing that usually detects *C neoformans*. Narayan et al[5] illustrated that latex agglutination test for serum cryptococcal antigen is only sensitive for the *C neoformans* species and yields false-negative results for *C albidus*. The latter can be cultured and differentiated from *C neoformans* by a phenol oxidase test (*C neoformans* is negative).[10] The sensitivity and specificity for *C albidus* using Tzanck test, Gomori methenamine-silver stain, Alcian blue stain, mucicarmine stain, India ink stain, and routine histology are unknown because of the relatively rare reports of human pathogenesis.[5,10] Similar to our case, there have been descriptions of cryptococcal infection diagnosed only by fungal culture with negative potassium hydroxide preparation and Gomori methenamine-silver stains. Hoang and Burruss[4] described a case of cutaneous-limited disease in a 14-year-old adolescent boy with psoriasis who developed a *C albidus* kerion while taking etanercept. Two consecutive skin fungal cultures were required to establish the diagnosis of *C albidus*.[4] In another instance, *C albidus* was only diagnosed with polymerase chain reaction analysis.[11] It is unclear why standard testing sometimes fails to demonstrate the organism. However, these cases demonstrate the importance of maintaining a high level of suspicion for fungal infection in immunosuppressed patients with persistent, atypical, unexplained plaques.

There are no clear-cut *C albidus* treatment guidelines due to limited reports.[12] Treatment failures have been described with amphotericin B and short courses of fluconazole (200 mg daily).[3] Suggested treatment regimens vary from 200 to 800 mg daily with durations ranging from 4 weeks to lifelong.[3-5] Delayed treatment response time, which can take up to 3 months, is thought to result from slow fungicidal action in immunosuppressed patients.[3] Even after discontinuing all systemic and topical immunosuppressants, our patient had a gradual response to fluconazole over several months.

In 2 large studies, efalizumab initially did not increase the risk for opportunistic infections over 36 weeks.[13,14] In October 2008, Genentech, Inc, and the US Food and Drug Administration issued a black-box warning of an increased infection risk, including progressive multifocal leukoencephalopathy, bacterial sepsis, viral meningitis, invasive fungal disease, and other opportunistic infections.[15] The medication was withdrawn from the US market in 2009.

A case report of possible efalizumab-related cryptococcal infection was published in 2007.[16] The patient did not have any opportunistic infections while on long-term therapy with methotrexate and cyclosporine. Twelve months after efalizumab was added to this regimen, an asymptomatic solitary cheek plaque of *C neoformans* appeared.[16] It is plausible that efalizumab could alter cell-mediated immunity against *Cryptococcus*.

Our case demonstrates the importance of maintaining a high level of suspicion for fungal infection in immunocompromised patients with persistent, atypical, unexplained plaques. In cases of *Cryptococcus* infections (not *C neoformans*), potassium hydroxide, periodic acid–Schiff, and latex agglutination for serum cryptococcal antigen testing might not suffice in establishing the diagnosis. It is prudent to obtain fungal cultures from the tissue in question, to evaluate for pulmonary involvement, and to consider brain imaging as well as lumbar puncture. If *Cryptococcus* infection is detected, antifungal medications typically are prescribed at high doses for prolonged courses with the guidance of infectious disease specialists. The dermatologist can play an important role in timely diagnosis of *Cryptococcus* infection because cutaneous involvement may precede systemic symptoms by 2 to 8 months and a biopsy can be obtained in a relatively expedient and noninvasive manner.[6-8]

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