Disseminated Cryptococcosis with Cutaneous Involvement due to *Cryptococcus gattii:* A Case Report

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ABSTRACT:
Disseminated cryptococcosis is a severe, life-threatening fungal infection caused by *Cryptococcus* species, with *Cryptococcus gattii* being a primary etiological agent in immunocompetent individuals. Rare but increasingly documented, cutaneous involvement in disseminated cryptococcosis can manifest as papules, nodules, ulcers, cellulitis-like or verrucous lesions. Here, we present a case of disseminated cryptococcosis with notable cutaneous involvement in an otherwise immunocompetent patient. The diagnosis was confirmed through fungal culture and histopathological examination, revealing typical *C. gattii* morphology. This case highlights the potential for *C. gattii* to cause systemic infection, including unusual cutaneous manifestations, in individuals without overt immunosuppression. This case also emphasizes considering cryptococcosis in the differential diagnosis of skin lesions, particularly in endemic regions or in patients with a history of environmental exposure. Early recognition and antifungal therapy are critical to improving outcomes, as cryptococcosis can rapidly progress to fatal multiorgan failure if left untreated.
Key words: Disseminated cryptococcosis, Cellulitis, *Cryptococcus gattii*

Introduction

Cryptococcus is an invasive fungus that causes cryptococcosis. *Cryptococcus neoformans* and *Cryptococcus gattii* are the two main species that cause infections in humans. While *C. neoformans* is most often associated with infections in immunocompromised patients, *C. gattii* is a less common but emerging pathogen that has been increasingly recognized in immunocompetent individuals[1,2,3]. Disseminated cryptococcosis occurs when the infection spreads beyond the lungs, affecting various organs such as the central nervous system, kidneys, liver, and skin. The most frequently affected organ in disseminated cryptococcosis is the central nervous system; however, cutaneous involvement is relatively rare and often poses a diagnostic challenge due to the nonspecific nature of its presentation[3]. Skin manifestations in disseminated cryptococcosis include papules, nodules, ulcers, and, more rarely, cellulitis-like or verrucous lesions, which may mimic other dermatological conditions[4,5,6].

This introduction outlines the clinical significance of disseminated cryptococcosis due to *C. gattii* with cutaneous involvement. Understanding the diverse clinical spectrum of *C. gattii* infection, including its rare skin manifestations, is critical for early diagnosis and appropriate antifungal therapy. Given the potential for severe outcomes, this report aims to increase awareness of cutaneous cryptococcosis as a presenting feature of disseminated infection and to encourage vigilance in its recognition and management.

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We reported a case of disseminated cryptococcosis with cutaneous involvement caused by *C. gattii* in a 73-year-old female who came with erythematous indurated plaques and ulcers on the right forearm and arm. Clinical and histological examinations revealed cutaneous cryptococcosis.

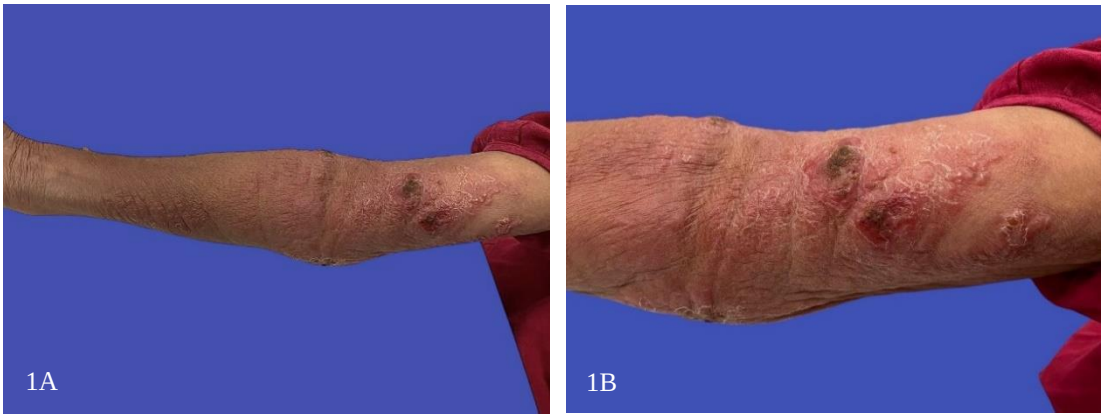

Figure 1A Localized, warm, ill-defined erythematous-indurated plaques with scales and ulcerated crusts on the right forearm and upper arm
Figure 1B Ill-defined erythematous-indurated plaques with scales and ulcerated crusts on the right upper arm

Case Report

A 73-year-old female from Bangkok presented to an outpatient clinic after one month of developing slow-growing, painful erythematous indurated plaques with ulcers on the right forearm and right arm. Five months prior, she was diagnosed with cellulitis in the same area and underwent a one-week treatment with intravenous ceftriaxone 2 g once daily and clindamycin 600 mg three times a day, which resulted in a clinical improvement. During this visit, she denies having experienced any local trauma, fever, headache, or respiratory symptoms. She did not have any risk factors for HIV infection. She denied receiving blood transfusions and intravenous drug use. She primarily cares for the elderly and gardens as a hobby. She lived in Bangkok and denied traveling to an endemic area. Her underlying conditions include thyroid cancer, first diagnosed in 1987. She received radioiodine therapy and was followed up by an oncologist every six months, with no recurrence found. She also has knee osteoarthritis. She has no history of intracellular organism infections and neutrophilic dermatosis. No family member who experienced the same condition as the patient and no history of malignancy in the family. A physical examination revealed the following vital signs: body temperature 36.8°C, blood pressure 129/64 mmHg, pulse rate 60 beats per minute, and respiratory rate 20 times per minute. She has localized, warm, ill-defined erythematous-indurated plaques with scales and ulcerated crusts on the right forearm and upper arm. (Figure 1A, 1B) There are no lymphadenopathies. The neurological examination revealed no abnormalities. The fundoscopic examination revealed no papilledema.

The incisional biopsy was performed on her right forearm and showed intraepidermal vesicles. The dermis showed marked dermal edema with numerous variable-sized yeasts with thick gelatinous capsules within large foamy and vacuolized histiocytes in the upper

and mid dermis. (Figure 2A, 2B) Tissue culture for fungus was positive for *Cryptococcus gattii.* Tissue cultures for aerobic bacteria and *Mycobacterium* spp. were negative. Polymerase chain reaction of tissue for Mycobacterium tuberculosis and non-tuberculous Mycobacteria was not detected. Anti-HIV was negative. The absolute CD4 count is 503 cells/µL (normal range: 470-1404 cells/µL). The CD4 percentage is 38% (normal range: 24-52%). Serum Cryptococcal antigen was positive 1:512, and hemoculture for fungus revealed *Cryptococcus gattii*. The molecular method used to identify Cryptococcus gattii is Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometer (MALDI-TOF MS). The cerebrospinal fluid profile was normal. Cryptococcal antigen, Indian ink, and culture for fungus from cerebrospinal fluid were negative. The computerized tomography of brain revealed no evidence of leptomeningeal enhancement, space-occupying lesions, midline shift, or brain herniation. The serum interferon-gamma level was in normal range. The results of the following laboratory tests, including a complete blood count and renal and liver function tests, are within the normal limit. The chest X-ray was normal. The overall studies suggest disseminated cryptococcosis with cutaneous involvement due to *C. gattii*. After discussion with an infectious disease specialist, she was treated with amphotericin B (1 mg/kg/day) and flucytosine (25 mg/kg) four times a day for two weeks in the induction phase, followed by oral fluconazole in the consolidation phase.

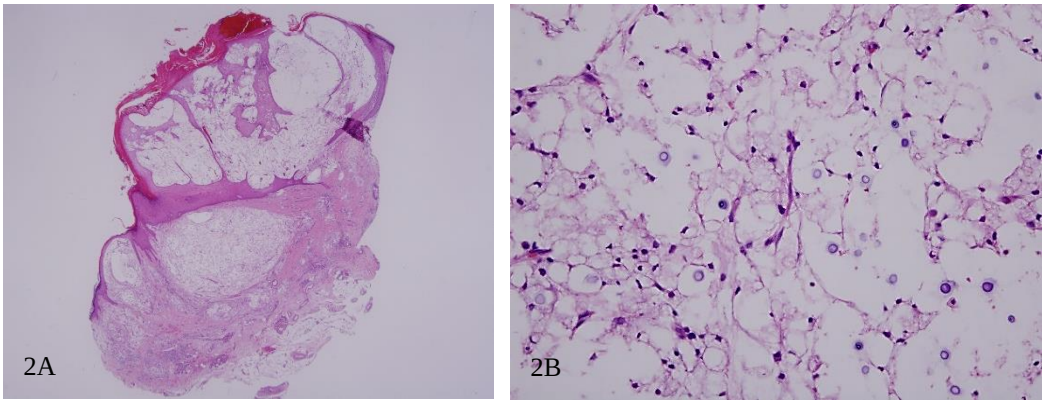

Figure 2A Epidermal hyperplasia, intraepidermal vesicle, mark dermal edema (H&E, X20)

Figure 2B Numerous variable-sized yeast with thick gelatinous capsule within large foamy and vacuolized histiocytes in dermis. (H&E, X400)

Discussion

Cryptococcosis is a widespread invasive fungal infection that can disseminate throughout the body. Cryptococcosis in humans is primarily caused by two species of fungi, which are *Cryptococcus neoformans* and *Cryptococcus gattii*. While *C. neoformans* is prevalent worldwide, mostly in soils contaminated by pigeon droppings and bird excreta, it primarily affects immunocompromised individuals, *C. gattii* infection often occurs in immunocompetent individuals and appears to be more virulent. It was found in various tree species, particularly in different types of eucalyptus. It has been confined to tropical and subtropical areas, including Southeast Asia, Australia, Brazil, Central Africa, Hawaii, and Southern California. Due to climate change, it has recently been detected in Vancouver Island,

parts of Europe, and the Pacific Northwest region of the United States[1,3]. *C. gattii* and *C. neoformans* are pathogenic yeast species but differ in morphology. Specifically, *C. neoformans* typically has thinner capsules compared to *C. gattii*. Capsule size can increase in vivo or in response to certain environmental stimuli. The capsules of *C. gattii* are thicker, which contributes to its increased virulence and often leads to higher long-term sequelae and mortality rates. In *C. neoformans*, the average diameter is 7.32 μm, and the mean capsule thickness is 5.5 μm. In contrast, *C. gattii* has an average diameter of 10.05 μm and a mean capsule thickness of 12.0 μm.[7,8] Inhalation of aerosolized infectious particles from *Cryptococcus* spp. is a recognized risk factor for the development of cryptococcosis. Skin infections commonly occur at sites of local skin trauma or from the spread of infection from other areas in the body.

Cryptococcosis predominantly affects the central nervous and respiratory systems in humans. Uncommon infections may involve the eyes, skin, prostate, or bones and joints. Although in immunocompromised individuals, the infection can spread broadly and affect various organs throughout the body. High-risk patients include those with hematologic malignancies, solid organ transplant recipients, immunosuppressive medication users (e.g. corticosteroids), advanced HIV infection, and CD4+ T lymphocyte levels < 200/mL.[1] Primary cutaneous cryptococcosis is a rare condition typically due to skin trauma, allowing direct inoculation of the yeast. Therefore, the appearance of cutaneous lesions is often considered a sign of possible disseminated infection. Skin lesions affect about 15% of patients with systemic cryptococcosis. Cutaneous manifestations range from acneiform papules or pustules that may develop into warty, vegetating crusted plaques with ulcers, as seen in our case. Additionally, firm-infiltrated plaques or nodules may suggest a systemic spread of the infection. Other presentations include cold abscesses, cellulitis, and nodular lesions. The infection frequently occurs in the extremities, with a higher prevalence in the upper limbs. In immunocompromised hosts, the infection often involves multiple areas or is confined to the lower limbs, whereas immunocompetent patients typically had infections on their fingers and faces[5,9].

Definitive diagnosis of cryptococcosis requires isolating *Cryptococcus* from clinical specimens or directly identifying the fungus using India ink staining of bodily fluids such as cerebrospinal fluid. Other methods for diagnosing cryptococcosis include serologic testing and histopathology of affected tissues[3].

For diagnostic purpose, culture on Sabouraud Dextrose Agar reveals that colonies of both species appear white. However, on Canavanine Glycine Bromothymol Blue Agar, colonies of *C. gattii* appear blue, whereas those of *C. neoformans* do not change color and remain yellow.

According to our patient's presentation, the lesions can resemble those caused by various infections; thus, performing a skin biopsy with culture and histological examination is crucial for a conclusive diagnosis. There are two different kinds of histologic reactions in cryptococcosis: granulomatous and gelatinous. Gelatinous lesions, as seen in our patient, presented with numerous organisms and minimal tissue reaction. Granulomatous lesions show more tissue reaction consisting of histiocytes and giant cells. The organisms were seen within the granuloma. Hematoxylin and eosin stains can detect Cryptococci. The capsule can be stained by using alcian blue, which shows a black color, and periodic acid-Schiff (PAS) stain, which shows a dark brown or black color[10,11].

Classifying the symptoms of the fungal infection is advised in order to help choose antifungal medications and establish the course

of therapy in accordance with the criteria for the diagnosis and management of Cryptococci. The symptoms are categorized into four groups, as follows: 1. Central nervous system cryptococcosis 2. Disseminated cryptococcosis 3. Isolated pulmonary cryptococcosis; and 4. Direct skin inoculation. After cutaneous cryptococcosis is identified, more testing is required to determine any dissemination. A positive hemoculture, tissue culture, and serologic test revealed that this patient had disseminated cryptococcosis with cutaneous involvement caused by *Cryptococcus gattii*[12].

Induction, consolidation, and maintenance are the three phases of antifungal medication used to treat cryptococcosis. For the induction phase of disseminated cryptococcosis, as in our patient, we recommend liposomal amphotericin B (3-4 mg/kg) and flucytosine 25 mg/kg four times a day for two weeks in a high-income setting, or liposomal amphotericin B 10 mg/kg single dose and two weeks of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily in a low-income setting. In the consolidation phase, use fluconazole 400–800 mg daily for 8 weeks. In the maintenance phase, use fluconazole 200 mg daily for 12 months. Direct skin inoculation can use fluconazole 400 mg daily for 3-6 months or until the lesion is clear. During treatment, one should monitor the side effects of drugs. Amphotericin B deoxycholate and liposomal amphotericin B can induce renal toxicity. Depending on the dosage, flucytosine side effects include hepatotoxicity, leukopenia, thrombocytopenia, and pancytopenia[12,13,14].

The prognosis for localized cutaneous infection in an immunocompetent host is favorable. However, if left untreated, secondary cutaneous cryptococcosis has a terrible prognosis with a mortality rate of up to 80%[9].

Our patient received treatment with amphotericin B (1 mg/kg/day) and flucytosine (25 mg/kg) four times a day in the induction phase. After one week of treatment, the patient developed leukopenia, a known side effect of flucytosine. As a result, flucytosine was discontinued and leukopenia was improved. Amphotericin B was continued and completed for a total of two weeks, followed by oral fluconazole in the consolidation phase. Unfortunately, while hospitalized, the patient developed kidney failure from septic acute tubular necrosis and died from bacterial septicemia.

In conclusion, disseminated cryptococcosis due to *C. gattii* is a serious and potentially fatal infection, particularly when it involves multiple organ systems, including the skin with various atypical skin presentations. Early recognition of this disease and prompt initiation of antifungal therapy are critical to improving patient outcomes.

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