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CASE REPORT

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A case of primary cutaneous Cryptococcus neoformans infection

Yan-jun Chu[1] and Jiong Zhou[1*]

Abstract

Background Cryptococcosis is an infectious disease caused by encapsulated heterobasidiomycete yeasts. As an opportunistic pathogen, cryptococcal inhalation infection is the most common. While Primary cutaneous cryptococcosis is extremely uncommon.

Case presentation A 61-year-old woman with a history of rheumatoid arthritis on long-term prednisone developed a red plaque on her left thigh. Despite initial antibiotic treatment, the erythema worsened, leading to rupture and fever. Microbiological analysis of the lesion's secretion revealed *Candida albicans*, *Pseudomonas aeruginosa*, and *methicillin-resistant Staphylococcus epidermidis*. Skin biopsy showed thick-walled spores, and culture confirmed primary cutaneous infection with *Cryptococcus neoformans*. Histopathological stains were positive, and mass spectrometry identified serotype A of the pathogen. The patient was treated with oral fluconazole and topical nystatin, resulting in significant improvement and near-complete healing of the skin lesion within 2.5 months.

Conclusions Primary cutaneous cryptococcosis was a primary skin infection exclusively located on the skin. It has no typical clinical manifestation of cutaneous infection of Cryptococcus, and culture and histopathology remain the gold standard for diagnosing. The recommended medication for Primary cutaneous cryptococcosis is fluconazole. When patients at risk for opportunistic infections develop skin ulcers that are unresponsive to antibiotic, the possibility of primary cutaneous cryptococcosis needs to be considered.

Keywords Primary cutaneous cryptococcosis, Cryptococcus neoformans, Immunocompromised, Fluconazole

Background

Cryptococcosis is an infectious disease caused by encapsulated heterobasidiomycete yeasts, specifically *Cryptococcus neoformans* and *Cryptococcus gattii*, which can infect the lungs, central nervous system, skin, and other body parts [1]. This fungus primarily affects immunocompromised individuals and is thus regarded as an opportunistic pathogen [2]. In 2003, primary cutaneous cryptococcosis (PCC) was confirmed as a distinct clinical entity, different from systemic cryptococcosis [3]. PCC is a primary skin infection caused by Cryptococcus species, occurring in both immunocompromised and immunocompetent hosts, often misdiagnosed due to its varied presentation [4, 5].

We reported a case of PCC in an immunocompromised patient with a long history of rheumatoid arthritis treated with prednisone. This study emphasizes the importance of considering PCC in the differential diagnoses of skin lesions in immunocompromised patients, highlighting the crucial role of histopathology and culture in diagnosis and the effectiveness of fluconazole in treatment.

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Case presentation

A 61-year-old female, approximately one month ago, developed a red plaque measuring 1 cm in diameter on the left thigh, which was hardness and elevated skin temperature. The local hospital gave levofloxacin and cephalosporin. However, the erythema gradually increased and ruptured (Fig. 1A), and fever emerged half a month prior, with the highest recorded temperature reaching 38.7℃. The patient had a 20-year history of rheumatoid arthritis and was currently on a daily prednisone dose of 15 mg.

Upon admission, her white blood cell count was 7.2*10^9/L, with a neutrophil percentage of 87.0%. C-reactive protein was elevated at 18.6 mg/L. Autoimmune serology revealed an antinuclear antibody (ANA) titer of 1:80 (++), anti-Ro 52 antibody ++, and anti-SSB antibody +++. Microbiological analysis of the skin lesion's secretion revealed the presence of *Candida albicans*, *Pseudomonas aeruginosa*, and *methicillin-resistant Staphylococcus epidermidis (MRSE)*. No fungal growth was found, and no *Mycobacterium tuberculosis* was found in the tuberculosis smear. PPD test, T-SPOT test, G-test, and GM test were all negative. Bacterial soft tissue infection was suspected, and the patient received different continuous antibiotic treatment regimens (moxifloxacin, cephalosporin+neomycin, linezolid), but the ulceration area increased after 10 days (Fig. 1B).

Considering the possibility of pyoderma gangrenosum or a connective tissue disease, methylprednisolone was initiated at 40-60 mg/day, and some antibiotics were discontinued. Unfortunately, the ulcer did not exhibit improvement (Fig. 1C).

Subsequently, a skin biopsy was performed, revealing thick-walled spores on histopathological HE staining (Fig. 2A, B), and PAS and PASM staining were positive. *Cryptococcus* was cultured on Sabourarud weak agar medium (Fig. 2C), and ink staining was positive (Fig. 2D). Mass spectrometry analysis showed serotype A, indicating Cryptococcus neoformans infection (the pathogen is *Cryptococcus neoformans*) [1]. Further investigations, including head MRI plain scan+DWI, lung HRCT, and other examinations, showed no evidence of systemic infection (Figs. 3 and 4). (The patient declined lumbar puncture due to severe osteoporosis.) Diagnosis of primary cutaneous Cryptococcus neoformans infection was made [4].

We rapidly reduced hormones to prednisone 15 mg/day. Simultaneously, treatment with oral fluconazole (0.4 g qd) and topical nystatin was started, supplemented by local hypertonic dressing, resulting in significant improvement in the patient's skin lesions within several days (Fig. 1D). After 3 weeks of antifungal treatment, the white blood cell count was 8.2*10^9/L, neutrophil percentage was 75.7%, and C-reactive protein was 1.9 mg/L.

The patient's skin lesions were basically healed after maintaining the above antifungal treatment for 2.5 months, and no evidence of extracutaneous infection was found during this period, which confirmed our diagnosis. At discharge, the white blood cell count was 7.5*10^9/L, and the neutrophil percentage was 68%.

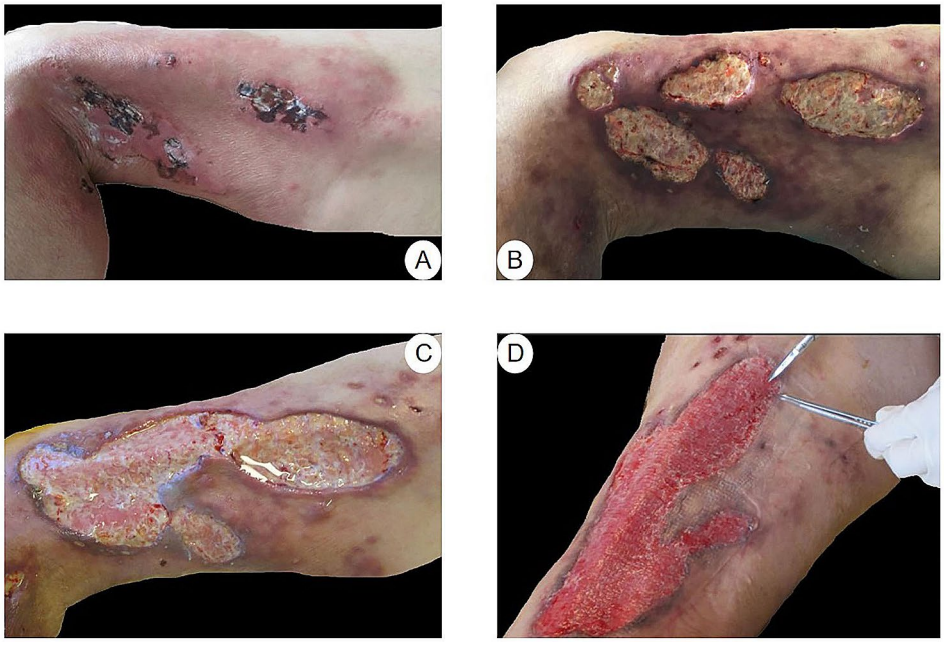

Fig. 1 Erythematous and ulcer on the outer side of the left thigh. (**B**) After 10 days of antibiotic treatment. (**C**) After 10 days of subsequent methylprednisolone treatment. (**D**) After 17 days of antifungal treatment, the secretions from the skin lesions were significantly reduced and the base surface was bright red

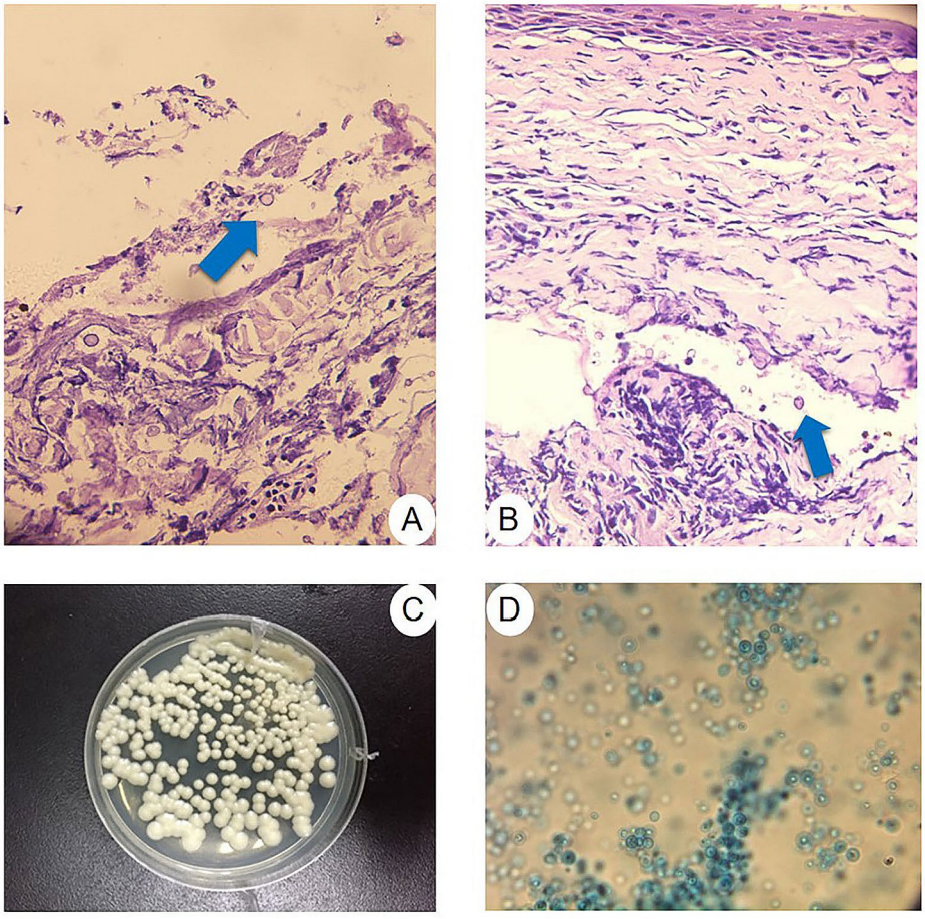

Fig. 2 (**A, B**) Skin biopsy showed thick-walled spores. (**C**) Cryptococcus culture positive. (**D**) Ink staining positive

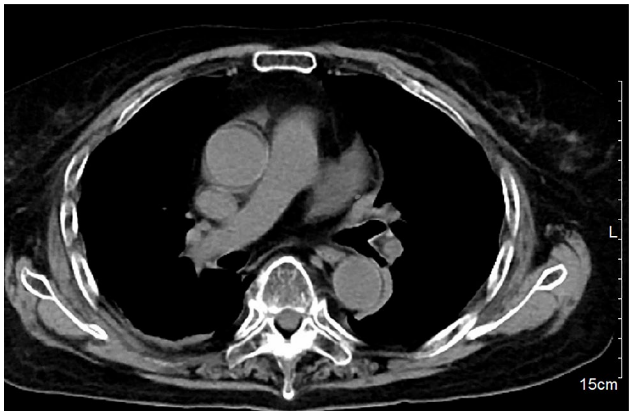

Fig. 3 Lung HRCT showed no evidence of infection

Discussion and conclusions

Primary cutaneous cryptococcosis (PCC) was identified as a primary skin infection exclusively located on the skin, different from systemic cryptococcosis [3]. PCC is diagnosed both in immunocompromised and immunocompetent hosts [5].

Cryptococcosis was thought to be caused by various forms of C. neoformans, which should include both *C. neoformans* and *C. gattii*, according to the new classification. These two species are classified separately based on phylogenetic studies and the absence of genetic recombination between them [5, 6]. *C. neoformans* is the main pathogen in immunocompromised individuals, while *C. gattii* typically affects immunocompetent individuals [7]. *C. neoformans* is further classified into *C. neoformans var. grubii* (serotype A) and *C. neoformans var. neoformans* (serotype D), which can interbreed, forming AD hybrids [8].

Human infection usually begins with the inhalation of environmental basidiospores or desiccated yeast cells, which reach the pulmonary alveoli [8]. The primary adaptive immune response to Cryptococcus involves the stimulation of CD4+T lymphocytes by dendritic cells, which secrete cytokines to recruit other lymphocytes and phagocytes to the infection site [7]. In immunocompetent hosts, antigen-presenting cells such as macrophages trigger cell-mediated immunity, leading to the elimination or containment of the fungi within granulomas [9].

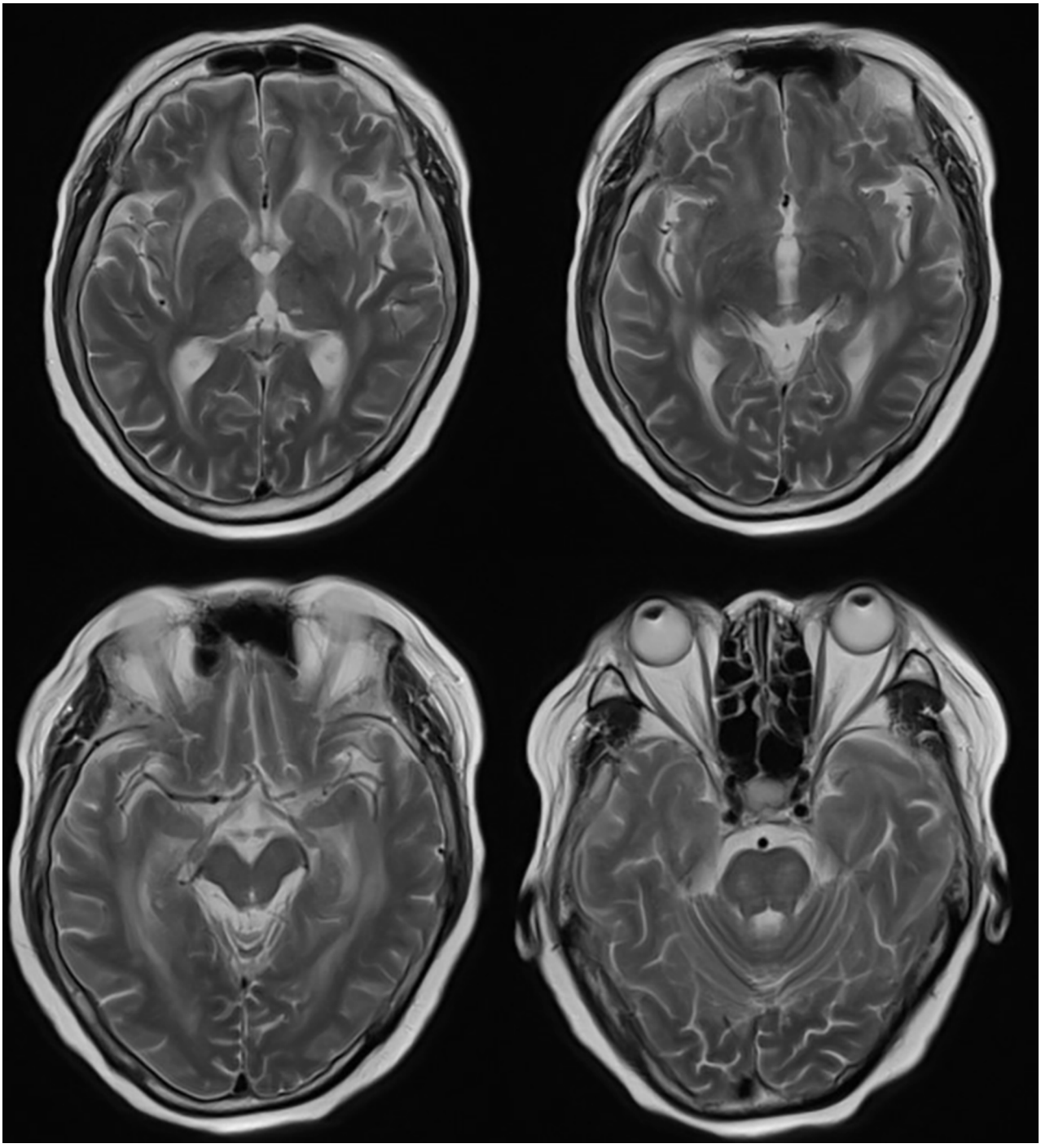

Fig. 4 Head MRI plain scan + DWI showed no evidence of infection

However, in immunocompromised individuals, such as those with impaired CD4+T cell function, the fungi can disseminate throughout the body, directly damaging immune cells and impairing the host's immune response. Those most vulnerable to cryptococcal infections include HIV-infected individuals, solid-organ transplant recipients, and patients on chronic corticosteroid therapy [10].

Cryptococcal infection can also occur through direct inoculation of fungal forms into the skin, a route commonly associated with farming activities [8]. PCC is diverse in presentation. It can present with a broad range of lesions, including ulcers, plaques, cellulitis, abscesses, pustules, papules, blisters, nodules [11]. It can mimic conditions like pyoderma gangrenosum, molluscum contagiosum, Kaposi's sarcoma, basal cell carcinoma, and

others, depending on the patient's HIV status [12]. Due to its diverse presentation, PCC cannot be diagnosed based on clinical manifestations alone; culture and histology remain the gold standards for diagnosis, although fine-needle aspiration has been suggested as a quick diagnostic method [5].

Treatment for PCC depends on the clinical form of cryptococcosis and the patient's immunological and overall health status [8]. The recommended treatment for PCC is fluconazole 400 mg daily for 3–6 months or until healed [13].

This case highlights the importance of considering PCC in immunocompromised patients. Culture and histopathology are crucial for diagnosis, and fluconazole is the preferred treatment. However, this case has several limitations. It is a single case study, limiting the generalizability of the findings. The patient's refusal to undergo a lumbar puncture due to severe osteoporosis prevented a thorough assessment of potential central nervous system involvement. Additionally, the treatment duration and follow-up were relatively short, leaving long-term outcomes and potential recurrence uncertain. Further studies with larger cohorts are needed to better understand PCC in immunocompromised patients.

Abbreviations

PPD test	Tuberculin purified protein derivative test
SPOT test	The T-SPOT test is a type of blood test used to diagnose tuberculosis (TB) infection. It works by detecting the presence of specific cells in the blood that react to TB antigens. This test is often used as an aid in diagnosing latent TB infection and active TB disease
GM test	Galactomannan test
MRI	Magnetic Resonance Imaging
DWI	Diffusion Weighted Imaging
HRCT	High resolution computed tomography
qd	Quaque die
PCC	Primary cutaneous cryptococcosis
MRSE	methicillin-resistant Staphylococcus epidermidis

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Author contributions
Jiong Zhou provided care for the patient and managed the case. Yan-jun Chu collected the data and wrote the manuscript. All authors read and approved the final manuscript.

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Data availability
Some or all data used during the study are available from the corresponding author by request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Zhejiang University School of Medicine Second Affiliated Hospital (No. 2024-0060).

Consent for publication
The patient has given written informed consent for her personal and clinical details along with identifying images to be published in this study.

Competing interests
The authors declare no competing interests.

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