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Disseminated Cryptococcosis Involving Skin and Lung in an Immunocompromised Patient After Kidney Transplantation: A Case Report

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Abstract: *Cryptococcus neoformans* can cause detrimental cryptococcosis and other severe complications, especially in immunocompromised populations. Disseminated cryptococcosis in organ transplantation patients is extremely rare and often involves lungs, brains, skin, nails, and other organs. In this paper, we report a rare disseminated cryptococcosis case involving skin and lung that presented with recurrent dark brown abscesses and nodules in an immunocompromised female after kidney transplantation. The K-Set detection result of *Cryptococcus* capsular polysaccharide in serum is positive. The identification of pus culture by Autof MS 1000 indicates that the patient was infected with *Cryptococcus neoformans* var. *grubii*. In addition to treatment using liposomal amphotericin B, fluorocytosine, and fluconazole, local extraction of pus and simultaneous injection of liposomal amphotericin B into skin lesions were performed. This comprehensive treatment method proved effective, as the patient recovered from fever and skin symptoms. The innovative treatment may contribute to helping more disseminated cryptococcosis patients.

Keywords: *Cryptococcus neoformans*; Disseminated cryptococcosis; Abscesses; Nodules

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1. Background

Cryptococcus neoformans, a globally distributed opportunistic fungal pathogen, is now ranked as the first fungal pathogen in the World Health Organization fungal priority pathogens list. *Cryptococcus neoformans*

typically originates from pigeon droppings and poultry habitats and can cause severe cryptococcosis and other complications [1]. This pathogen is classified into two varieties: *C. neoformans* var. *neoformans* and *C. neoformans* var. *grubii*. The mortality rate associated with cryptococcal infection is significantly high, particularly among immunocompromised patients, such as those with human immunodeficiency virus (HIV), organ transplant recipients, and long-term users of immunosuppressants [2,3]. The lungs are the most commonly affected site of infection, with *Cryptococcus neoformans* disseminating to various parts of the body through hematogenous route. Skin, nails, and other organs are less commonly involved, and primary skin infection is relatively rare.

This paper describes a case of disseminated cryptococcosis in an immunocompromised patient after kidney transplantation, presenting with multiple recurrent abscesses and nodules affecting the skin and lungs.

2. Case presentation

A 38-year-old female presented with a one-month history of progressively increasing multiple dark brown abscesses and nodules. One month prior to this, sporadic brown bean-sized to egg-sized abscesses and nodules appeared on her limbs, accompanied by mild itching and exudation, progressively increasing over time (**Figure 1**).

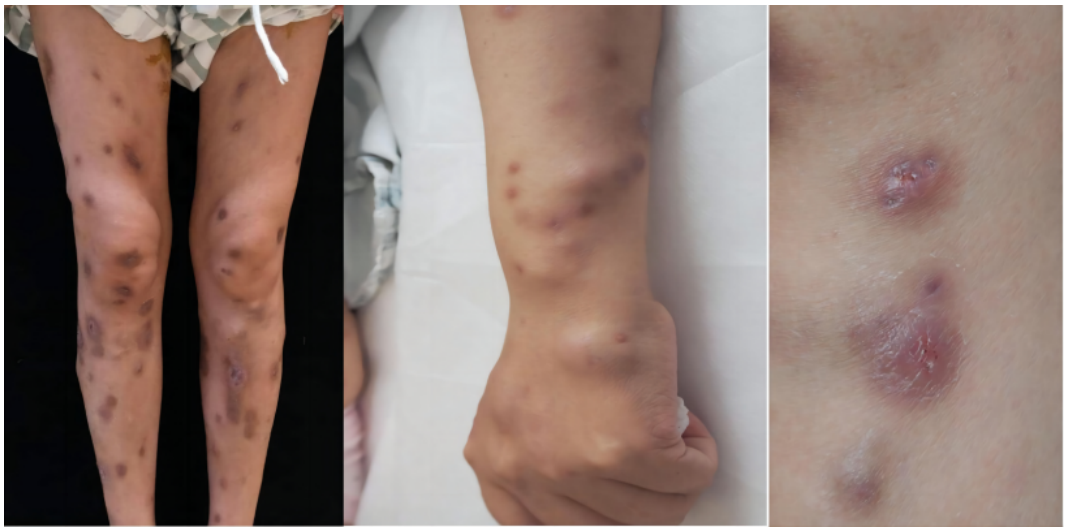

Figure 1. Dark brown abscesses and nodules on the limbs, with diameter varying from 5 mm to 2 cm

Two months before the current presentation, the patient had a fever and cough with no obvious cause. The alveolar lavage fluid smear showed cryptococcal infection and the blood metagenomic next-generation sequencing (mNGS) indicated cryptococcosis. The patient received right kidney transplantation 11 years ago, but the right kidney was damaged due to COVID-19. Following that, she underwent regular hemodialysis for eight months and had accompanying renal anemia and renal hypertension.

Upon admission to our hospital, several examinations were performed. Computed tomography (CT) of the chest discovered presence of nodules in the right lung indicating possible cryptococcal granuloma; presence of multiple small nodules in both lungs; scattered fibrous foci in both lungs; and mediastinal lymph node enlargement (**Figure 2a**). Abdominal B-ultrasound found right kidney atrophy and presence of cyst in the right kidney. Magnetic resonance imaging (MRI) of the head showed multiple abnormal signals in the brain, consistent with inflammation, and bilateral basal ganglia with point-like acute infarction. Ocular color Doppler

ultrasound and optical coherence tomography (OCT) found retinal detachment in macular area of the right eye, papillary edema, 10 cm anterior index distance of right eye (**Figure 2b**).

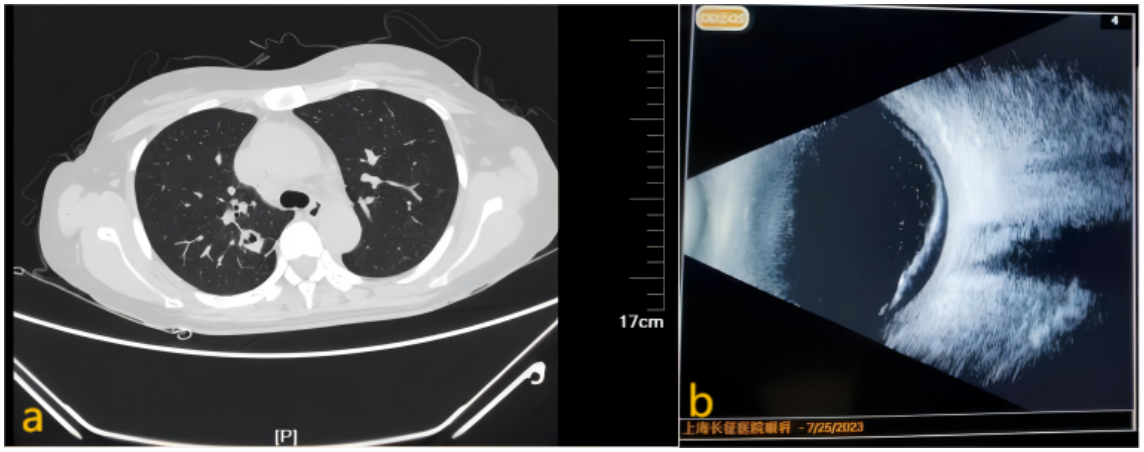

Figure 2. (a) Nodules of right lung (b) Retinal detachment in macular area of right eye

The result of cryptococcal capsular polysaccharide detection K-Set (Genobio Pharmaceutical Co., Ltd., Tianjin, China) was positive with a titer of 1:640 (**Figure 3**) in serum.

However, no cryptococcal evidence were found in cerebrospinal fluid-related tests, including capsular polysaccharide detection, direct microscopy, and fungal culture.

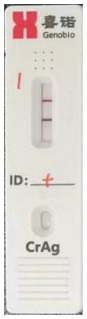

Figure 3. Cryptococcal capsular polysaccharide detection K-Set, lateral flow assay

Biopsy of a newly emerging abscess revealed many caseating granulomas over the entire skin field. Subcutaneous ulcers and chronic suppurative inflammation were found by special staining of *Cryptococcus* spores, with capsulated fungal yeast-like cells seen in the abscess (**Figure 4**).

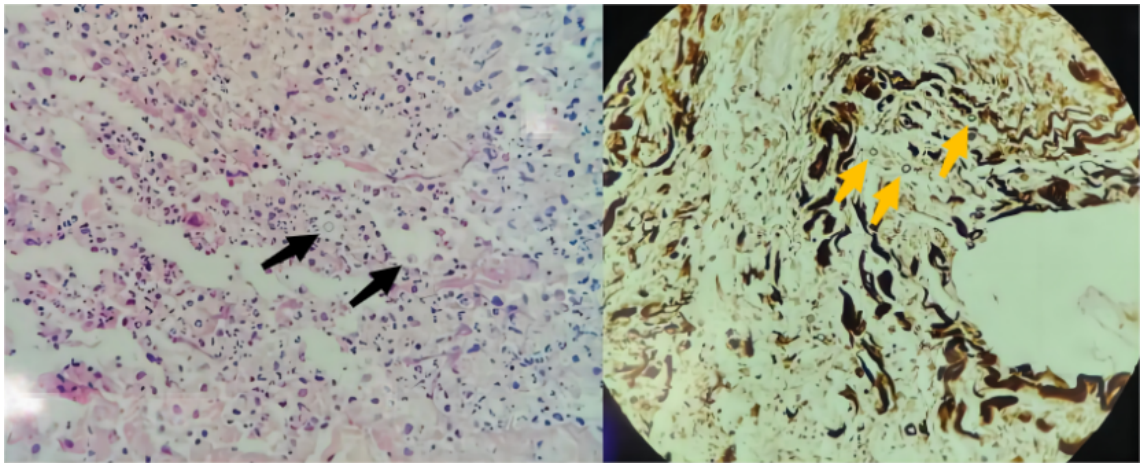

Figure 4. *Cryptococcus* spores can be seen in the abscess

Direct microscopy of skin pus using India ink staining and Trypan blue staining was positive (**Figure 5**). Inoculation of the pus was carried out, the result of direct microscopy and culture revealed *Cryptococcus neoformans* var. *grubii*, which was also confirmed by Autof MS 1000 (Autobio Diagnostics Co., Ltd., Zhengzhou, China) (**Figure 6**). The *Cryptococcus neoformans* var. *grubii* was preserved in Microbiome Research Center, Moon (Guangzhou) Biotech Ltd., with strain number MN151897.

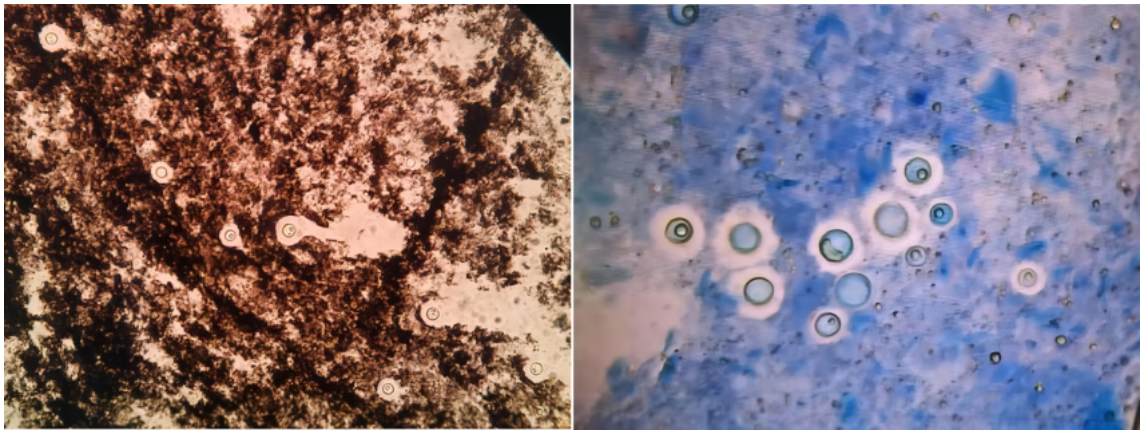

Figure 5. India ink staining and Trypan blue staining of the skin pus

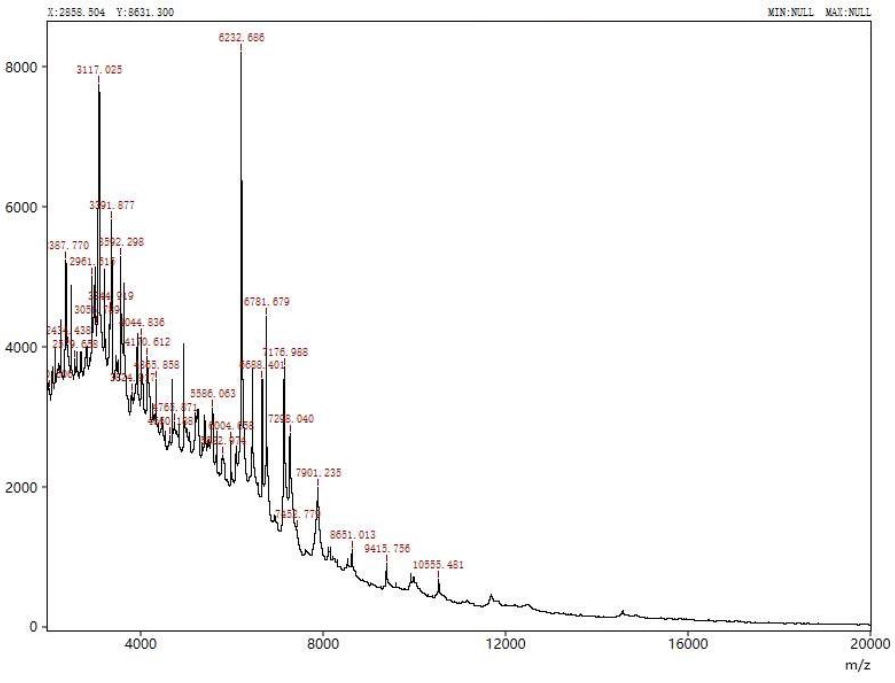

Figure 6. Autof MS 1000 mass spectrometry of *Cryptococcus neoformans* MN151897

Laboratory testing revealed a C-reactive protein (CRP) concentration of 78 mg/L, an erythrocyte sediment rate of 80 mm/h and a negative result of HIV serology test. $CD4^+$ T cell count and the levels of white blood cells and neutrophil were normal. T-SPOT.TB test, (1,3)-β-D glucan (G test), and galactomannan (GM test) were all negative. Other laboratory results were unremarkable.

According to the results of correlated laboratory findings and symptoms of the patient, liposomal

amphotericin B (100 mg intravenous drops every day), fluorocytosine (1 g orally every other day), and moxifloxacin (0.4 g orally every day) were given for 3 weeks. During this period, her fever and cough resolved. However, the abscesses and nodules progressed sporadically, thus we adopted a treatment method of local extraction of skin pus and simultaneous injection of liposomal amphotericin B into the skin lesion (**Figure 7**).

Figure 7. A novel treatment method of local extraction of skin pus and simultaneous injection of liposomal amphotericin B into the skin lesion

Twenty days later, the patient's blood latex agglutination test was 1:80, and liposomal amphotericin B was then replaced by fluconazole (400 mg orally every day). Ten days later, the patient's blood latex agglutination test reduced to 1:60. No newly emerging abscesses or nodules were noted, while all pre-existing skin abscesses and nodules were reduced, smoothed, and diminished (**Figure 8**). Other symptoms were also resolved. Finally, the patient was discharged from our hospital with fluconazole (150 mg orally every day) and recommended for regular clinical follow-up. One month later, the patient displayed no recurrent skin symptoms.

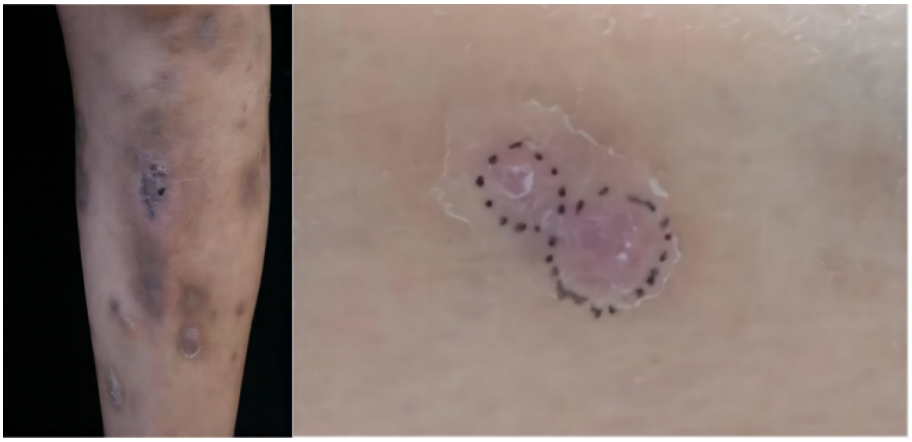

Figure 8. Pre-existing skin abscesses and nodules were reduced, smoothed, and diminished after treatment

3. Discussion and conclusion

Cryptococcus neoformans often causes severe diseases, primarily in the HIV pandemic. The main predisposing factors include organ transplantation, long-term corticosteroid use, cancer radiochemotherapy, and antibiotic abuse [4,5]. As a major threat to global health, *Cryptococcus neoformans* is responsible for more than 15% of

deaths among HIV-infected patients [4]. Environmental exposure is prevalent in the public, as it can either be eliminated or colonized in human body [6]. Deadly disseminated cryptococcosis, mainly resulting from lung infection and disseminating to various body sites through a hematogenous route, occurs primarily in immunocompromised patients [7]. Disseminated cryptococcosis in organ transplantation population is extremely rare and usually involves the central nervous system [8-10].

In our case, the patient was HIV-negative but immunocompromised due to kidney transplantation. The patient primarily presented with recurrent multiple abscesses and nodules caused by *C. neoformans* var. *grubii*, without cryptococcal meningitis. To the best of our knowledge, there have been reported cases of extra-pulmonary cryptococcal infection presenting with abscesses and nodules [10,11], but few of them have demonstrated a recurrence of soft-tissue infection similar to that observed in our patient.

Initially, the patient was diagnosed with pulmonary cryptococcal infection. Subsequently, her cutaneous infection appeared as a manifestation of disseminated cryptococcosis, which has been reported in similar case studies [10-12]. Generally, disseminated cryptococcosis can present with various skin manifestations, including not only abscesses and nodules but also ulcers, vesicles, granulomas, purpura, pustules, and even draining sinuses and cellulitis.

The confirmatory diagnosis of disseminated cryptococcosis often relies on the detection of cryptococcal capsular polysaccharide in serum [13]. However, in other similar cases [9-11,14-16], some clinical samples such as pus, sputum, and tissues from lesion sites may not be suitable for serological testing. However, these clinical samples still play an important role in the timely diagnosis of cryptococcal infection. It can be seen that using a combination of multiple testing methods is necessary and advantageous in the diagnosis and subsequent treatment guidance of disseminated cryptococcosis.

In this case, the appropriate combination of molecular biology, Autof MS 1000, and classical detection methods provides strong support for the rapid diagnosis and determination of subsequent treatment plans. The result of metagenomic next-generation sequencing (mNGS) help clinicians understand the overall condition of the infection and promptly exclude the possibility of multiple infections. The integration of Autof MS 1000 and traditional bedside culture methods enables quick determination of the causative agent of the patient's infection, which was the specific strain of *C. neoformans* var. *grubii*.

However, even though *Cryptococcus* can be easily cultured on routine fungal culture media, the post-medication positive rate is greatly reduced, which poses certain difficulties for a detailed analysis of treatment effects [5, 17]. Additionally, this case has highlighted the necessity for further development of new molecular biology methods in the future. For instance, methods for obtaining high-quality DNA from samples such as pus, specific primers for rapid *Cryptococcus* typing, and isothermal amplification systems that are both cost-effective and faster than real-time quantitative polymerase chain reaction (PCR), among others [18,19].

Therapy for disseminated cryptococcosis in immunocompromised patients has shown success in most cases [14]. Systematically using liposomal amphotericin B remains one of the recommended treatment options according to current guidelines both domestically and internationally [17]. However, in our patient's case, despite receiving 100 mg/day of liposomal amphotericin B for 3 weeks, there was limited improvement and new skin symptoms emerged instead. Notably, we implemented a new treatment approach of locally extracting skin pus and simultaneously administering liposomal amphotericin B into the skin lesion. Our innovative treatment approach proved effective in controlling the disease's progression and significantly reduced the abscesses and nodules. Therefore, based on its therapeutic effectiveness, our novel treatment method of local extraction of skin pus and simultaneous injection of drugs into skin lesions can be promoted for the better treatment of disseminated cryptococcosis involving the skin or primary skin cryptococcosis.

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Disclosure statement

The authors declare no conflict of interest.

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