A Late-Onset Disseminated Cryptococcal Infection after Renal Transplantation

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ABSTRACT

Cryptococcus neoformans is an encapsulated yeast in the natural environment, and soils often contaminated with bird droppings are the most important source of contamination. In this article, a 61-year-old female recipient of renal transplantation, who was diagnosed with disseminated cryptococcal infection with skin involvement, is presented. Physical examination of the patient was found to have atypical lesions on her face. At the end of the 72-hour incubation of the scraping sampling from the patient's lesion; Crytococcosis was diagnosed by detecting encapsulated yeast fungi in staining with Indian ink. Yeast structures compatible with C.neoformans were seen. L-Amphotericin B treatment, which was started. The patient died on the 8th day of follow-up despite extensive and effective antifungal therapy. In conclusion, it should be considered that opportunistic fungal infections that may develop due to the use of immunosuppressive agents in patients undergoing solid organ transplantation.

KEYWORDS: *Cryptococcus neoformans*; Renal transplantation; Fungal infections

INTRODUCTION

Cryptococcus neoformans is an encapsulated yeast in the natural environments, such as soils, plants, or foods that are often contaminated with bird droppings are the most critical source of contamination [1,2]. *C. neoformans* is transmitted to humans by inhalation. A microorganism which is taken by inhalation may spread hematogenously and/or lymphogenously from the lungs to the body and causes central nervous system, bone, and skin infections [1,3]. Immunity against Cryptococcal infections is provided by T-cells. Depending on this, the incidence of Cryptococcal infections increases in patients with suppressed cellular immunity. It is often seen in HIV-infected people, donors of solid organ transplants (SOT), and patients using a long-term Corticosteroid [2].

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Cryptococcal infections are the 3rd most common fungal infection in SOT recipients after candidiasis and aspergillosis [2,4,5]. Cryptococcal infections may appear as primary infections or reactivation of latent infections [1]. According to epidemiological studies, cryptococcal infections are thought to develop with the reactivation of latent infection. The disease is usually seen within one year after transplantation [5]. This research presents a patient with renal transplantation who was diagnosed with disseminated cryptococcal infection and related skin involvement.

CASE PRESENTATION

A 61 years old female patient registered to emergency services with complaints of coughing, fever, sputum, and variable consciousness. From the patient's story, it is learned that she was diagnosed with hypertension and had renal transplantation four years ago. She is under treatment with Microphenolic acid, Tacrolimus, and Metyl-prednison for immunosuppression. Also, it was detected that she applied to another hospital with a complaint of cough, sputum, and shortness of breath two months

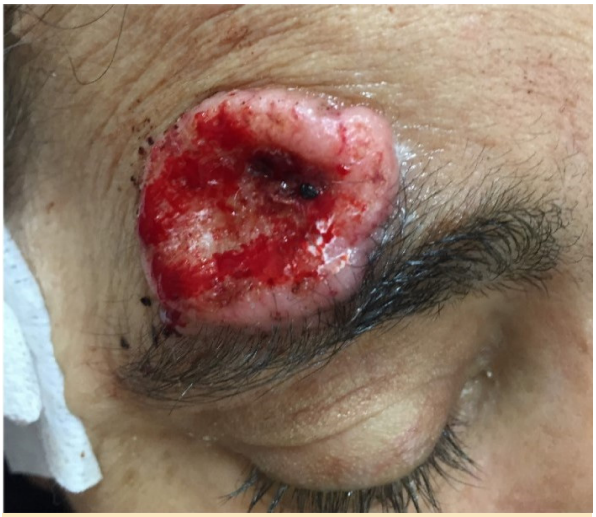

Figure 1: In the head and neck examination, there were lesions pitted in the middle and hypertrophic around her right eyebrow lateral.

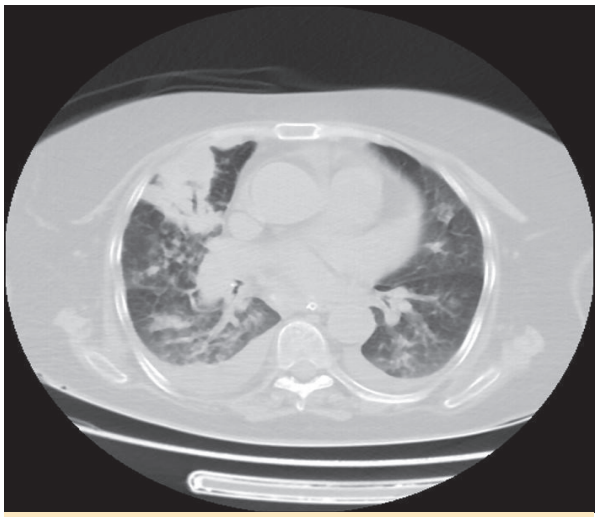

Figure 2: In the thorax CT, patchwork-like reticulonodular infiltration fields in bilateral lungs and sporadic frosted glass density fields was observed.

ago. In hospital, her thorax was scanned by computed tomography (CT), and with these CT results, it was learned that the transthoracic biopsy was applied with the suspect of bulk in the lungs. As a result of pathologic investigation, yeast elements were seen, and the Liposomal Amphoterisine-B (L-AMB) treatment was implemented for seven days. Nevertheless, in those times, with the the patient's and her family's demand, she was discharged from the hospital, and the treatment was not completed. When she applied to our hospital emergency service, her general situation was terrible and her consciousness was confused.

In physical examination, the temperature was 36°C, blood pressure was 140/72 mmHg, oxygen saturation was 85%, and pulse was 97/minute. In the head and neck examination, there were lesions pitted in the middle and hypertrophic around her right eyebrow lateral and her mandible (Fig. 1). Also, rigidity was detected in the nape. In the respiratory system examination, by listening to bilateral lung basals, ral and ronkus was heard. There was no pathology in the abdomen examination. C-reactive protein (CRP) was 159 mg/dL, leukocyte was 8630/µL, thrombocyte was 260000/µL, and creatinine was 1.1 mg/L in a blood test at the laboratory analysis. The patient was followed with intense care conditions. The treatment was started as follows:

L-AMB 10 mg/kg as empirical once in a day (1x1) intravenous (iv), Posaconazole 600 mg 1x1 iv (induction dose), 300 mg 1x1 iv (maintenance dose), Meropenem 1 gr 3x1 iv, Linezolid 2x1 iv.

Thorax-CT and cranial magnetic resonance imaging (MRI) were taken from the patient. In the thorax-CT investigation, pleural effusion and collapse/consolidation fields in the lung parenchyma close to the effusion was seen. Also, in the middle lobe, there was a consolidation field, including an air bronchogram which was located from the hiler region to the anterior subpleural distance. Moreover, patchwork-like reticulonodular infiltration fields in bilateral lungs and sporadic frosted glass density fields was observed (Fig. 2). In the cranial MRI, nodular T2-based hyperintense with sporadic merge tendency was observed in bilateral basal ganglia and mesencephalon left crus cerebri. Hyperintense was also seen in FLAIR A. In T1-based images, many pathologic signal varieties of hypointense takes attention. Again, in the lesion where the level of mesencephalon left crus cerebri, minimal peripheral contrast was seen (Fig. 3). The image was evaluated as brain involvement of disseminated infection.

Furthermore, in the level of corona radiata

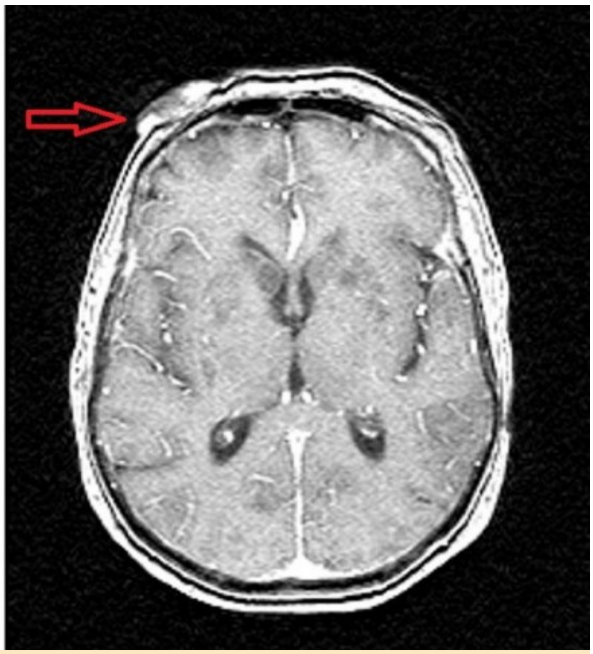

Figure 3: In the cranial MRG, in the level of corona radiata and left frontal region of scalp, signal changes compatible with lipoma at first sight and a partial light hypertense sized 26x20 mm in T1 and T2-based images was observed.

and left frontal region of scalp, signal changes compatible with lipoma at first sight and a partial light hypertense sized 26x20 mm in T1 and T2-based images was observed (Fig. 3).

The sample taken from the right eyebrow lateral lesion was evaluated using Gram staining and KOH test, and yeast-like structures was seen. Skin scraping sample is sowed to media with SDA (w or w/o Cycloheximide) and 5% sheep blood and incubated at 37°C. After 72 hours of incubation, Gram staining and Indian ink was applied from SDA without Cycloheximide and from the white-cream colonies without hemolysis that existed in bloody agar. Prediagnosis of Cryptococcosis was determined by detecting capsulled yeast with Indian ink. *Cryptococcus neoformans* was determined by using the Vitec2 (Biomerieux, France) determination – antifungal sensitivity cards. It was sensitive to Amphotericin B. L-AMB treatment, starting with patient hospitalization, was continued. On the 2nd day of hospitalization, a lumbar puncture was performed, 2-3 mL cerebrospinal fluid was collected, and sent

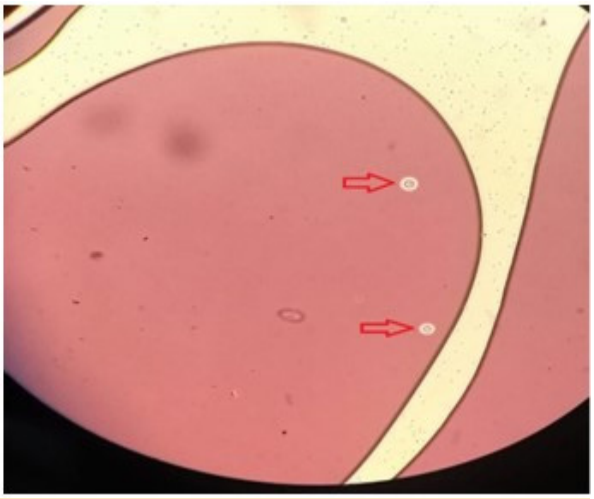

Figure 4: Indian ink were implemented to the CSF. Yeast alike structures were seen following *Cryptococcus neoformans*.

for biochemical, microbiological, and cytological analyses. The appearance of cerebrospinal fluid was clear. In the microscopic investigation of cerebrospinal fluid, 50 leukocytes/mm3 was seen; approximately 75% of them were polymorphonuclear, and 25% were lymphocyte appearance. Cerebrospinal fluid for microbiologic investigation was centrifuged at 3000 rpm/min for 5 min. After centrifuge, supernatant culture (bloody agar and SDA) and dying (gram and Indian ink) were implemented. Yeast alike structures were seen following *Cryptococcus neoformans* (Fig. 4). Detected yeast in cerebrospinal fluid culture is determined as Cryptococcus neoformans by using the Vitec2 yeast chart. On 6th day of treatment, the general situation of the patient broke down. Oxygen saturation decreased in arterial blood gas. The Patient was discharged on the 8th day of treatment in a stable condition.

DISCUSSION

Cryptococcus neofromans is a capsulated opportunist fungal pathogen that is often presented in natural environments, and is contagious from bird droppings, soil, plants, dust, and contaminated food.1 It is reported that risk factors of *C. neoformans* infections are deterioration of cellular immunity, steroid and chemotherapeutic usage, SOT, broken humoral immunity, and direct or indirect encounters

with pigeon droppings [3].

The main reasons for mortality and morbidity are many infections, including fungal infections, which developed dependingly long term immunosuppressive treatments for preventing graft rejection in the SOT receivers [6]. It is thought that glucocorticoids increase susceptibility to *C. neoformans* infections by decreasing cellular immunity in SOT receivers [7]. Calcineurin inhibitors like tacrolimus inhibit related fungal infections at 37°C. Nonetheless, it doesn't impede at 24°C. This specific condition shows that Calcineurin inhibitors could decrease CNS infections and let fungal infections development in the peripheric sides, like skin and regions with lower temperatures [1,8]. In our case, the patient's long-term calcineurin inhibitor treatment plays a role as a predisposing factor in developing a cryptococcal infection. Also, calcineurin inhibitors were unsuccessful in preventing developing CNS infections.

Fungal infections account for approximately 5% of SOT receivers-related infections [6]. In SOT recipients, Cryptococcal infections rank 3rd among the most common fungal infections with an average incidence of 1.8% [5]. Cryptococcal infections are generally seen one year after transplantation in SOT receivers [2,5]. Recently, in a surveillance study that was considered cryptococcal infections in SOT receivers, it was observed that the mean onset time of infection in 75% of patients developed earlier than three years after transplantation [2]. But in our case, the disease starting time was four years after transplantation. According to epidemiological studies, it is thought that latent infection's reactivation developed instead of newly developed infection [1,5].

C. neofromans firstly infects the lungs. From the lungs to the body, spread happens hematogenous and/or lymphogenous. It causes often central nervous system infections. Cutaneous, mucocutaneous, osseous, and visceral infections were rarely seen [3]. Cryptococcal skin involvement occurs in disseminated disease and is known to be seen in different ways. It can be shown as an acneiform papule, ulcer, subcutaneous nodule, and rarely cellulite-like lesions. Although hematogenous cryptococcal skin changes can be of any kind of morphology, they are classically seen as molluscum contagiosum-like umbilical lesions [1]. In our case, besides CNS and pulmonary infections, there were umbilical skin lesions determined by Charadeo *et al.* Also, cranial imaging suggests that the CNS involvement can be opened to the skin through neighboring, destructing the cranial bones rather than the hematogenous spread of the skin lesion.

Correct and timely diagnosis is effective in the treatment of cryptococcal infection. Diagnosis was realized through showing antigen or C.neoformans capsule [9]. As seen in Fig. 4, capsulled yeast structures of C.neoformans was observed with the scraping sample from a skin lesion and Indian ink staining from cerebrospinal fluid.

Antifungal treatment must include induction, consolidation, and protection phases to reduce relapse risk and exact cure of the disease.8 Suggested therapy for disseminated cryptococcal infection and meningoencephalitis includes L-AMB 4 mg/kg per day, Flucytosine 2.5 gr 3x1, and Fluconazole 200/400 mg per day during two weeks induction treatments and later on and consolidation treatment at least 6 months [5,8]. Antifungal prophylaxis regimen can vary according to the institution. Antifungal prophylaxis regimen in SOT recipients was evaluated in a meta-analysis of 14 randomized studies with 1497 patients. According to this evaluation, it was reported that antifungal prophylaxis did not decrease mortality. In addition, it is reported that the use of prophylactic antifungals is problematic, especially due to the interaction of azole group antifungals with immunosuppressant agents [6].

In conclusion, because of the high mortality of opportunistic infections developing with the usage of immunosuppressive agents on SOT receivers, history and physical examination should be taken carefully and immediately treated with an exact diagnosis and appropriate drugs.

CONFLICTS OF INTEREST: None declared.

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