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Case Report
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CNS Phaeohyphomycosis in Post-Transplant Patients: Two Cases Report

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Abstract

Phaeohyphomycosis is a fungal infection caused by dematiaceous or melanized fungi. These fungi are distinguished by the predominance of melanin in the cell wall, which acts as a virulence factor. They are ubiquitous in the environment, and it can be transmitted through inhalation. Phaeohyphomycotic processes may be superficial, subcutaneous, or deeply invasive or disseminated. Invasive diseases (including deep local infections, pulmonary infection, cerebral infection, and disseminated disease) are uncommon. Although, they are associated with high mortality, as they can cause severe illness in both immunocompetent and immunocompromised individuals. Diagnosis can be made through mycological, histopathological, or molecular techniques. Treatment typically involves surgery or systemic antifungal medications. Here, we report two cases of CNS phaeohyphomycosis, both with post-transplant patients on immunosuppressant.

Keywords: Phaeohyphomycosis, Dematiaceous, Liposomal Amphotericin B

First Case

A 38-year-old Omani male who had had Hypertension, chronic kidney disease underwent renal transplant, kept on immunosuppression medication (Tacrolimus, Mycophenolate mofetil and prednisolone). He was admitted to the Department of Neurology, khoula hospital, Oman, and presented with history of vomiting and loss of consciousness at home. Two days previously, he had pain in both upper and lower limbs. The first computed tomography (CT) scan of the brain demonstrated a mass lesion, an ill hypodense area in the right parietal posterior aspect subcortical white matter, suggestive of non-hemorrhagic infraction. Figure 1

Full laboratory blood analysis revealed a hemoglobin level of 11.8 g/dl; white blood cells, serum electrolytes, and liver function test results were within normal ranges. Blood cultures were sterile. MRI (Magnetic Resonance Imaging) brain scan done and suggestive of cerebral abscess in the parietal lobe, atypical infection to be considered because of the intrinsic blooming artefact in the lesion. Lumber puncture done showed normal analysis and microscopy. CSF (Cerebrospinal Fluid) culture normal. Other investigations included HIV (Human immunodeficiency viruses), tuberculosis, cryptococcus, CSF viral panel and fungal culture were all negative. Patient started on Meropenem and vancomycin empirically to cover for possible bacterial infection and decided to repeat Brain MRI after 4 weeks. During this duration, the patient was free seizure, afebrile, hemodynamically stable, has headache occasionally, no vomiting. After 4 weeks, brain MRI were repeated showed remarkable increase in the size of the right parietal abscess with evidence of projection like appearance of the inner wall of the abscess and some areas of shaggy wall enhancement concerning for possible fungal etiology.

Neuosurgical intervention consisted of a right parietooccipital craniotomy and excision of the right posterior parietal abscess.

The material was analyzed by microbiological and histopathological laboratory.

Microscopic examination of the biopsy sections (pus tissue) stained with H&E stain (hematoxylin and eosin stain) revealed necrosis with dense and diffuse mixed inflammatory infiltrates. There were multiple foci of granulomatous inflammation, micro abscesses and micro/macro-necrosis. The granulomas show multinucleated giant cells some of which showed pigmented septate branching fungal hyphae and conidia. The pigmented fungal hyphae are also seen in the brain parenchyma close to area of necrosis and micro abscesses. Other special stains like GMS (Grocott methenamine silver) and PAS (Periodic acid-Schiff stain) showed septate branching fungal hyphae and conidia. Fungal melanin pigment was not seen on those stains as on H&E stain. The tentative diagnosis of CNS phaeohyphomycosis diagnosis was made. Patient started on liposomal amphotericin B and voriconazole.

The clinical specimen was cultured on sabouraud dextrose agar at 30 to 35°C. Growth of melanized fungi after 1 week was observed as showed in figure 2, brown to blackish colony with high-domed centre and submerged margin. These fungi were morphologically classified as Rhinocladiella mackenziei.

Microscopic studies using slides were prepared from these cultures in lactophenol cotton blue under biosafety level 3 regulations, showed smooth, pigmented, septate hyphae with brown conidia.

DNA was extracted, internal transcribed spacer (ITS) ribosomal DNA was amplified using primers and sequenced with the internal primers. PCR amplification and sequencing were performed and compared with entries in a molecular database. The isolate was identified as Rhinocladiella mackenziei.

The molecular results confirmed the mycological diagnosis, and histopathological observation led to the diagnosis of cerebral phaeohyphomycosis due to Rhinocladiella mackenziei.

For the management of the case, patient treated with both liposomal amphotericin B and voriconazole. Simultaneously, empirical antibacterial therapy, consisting of Meropenem and colistin was initiated. As there is no improvement and based on the the new finding of the abscess showed in brain CT scan, he underwent another craniotomy and excision of the abscess. Despite amphotericin B with voriconazole therapy and surgical management, the patient's condition continued to deteriorate, and he expired 6 weeks after diagnosis of the disease.

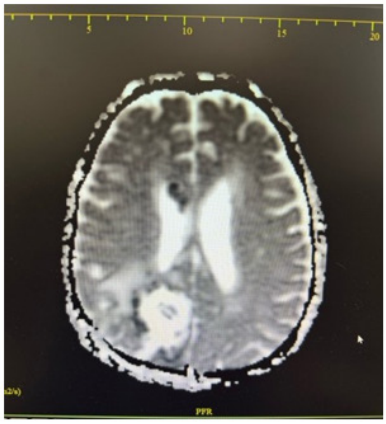

Figure 1: A computed tomography scan of the brain demonstrated a mass lesion.

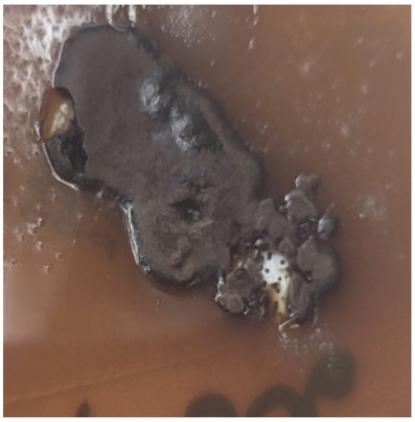

Figure 2: Fungal culture morphologically classified as Rhinocladiella mackenziei

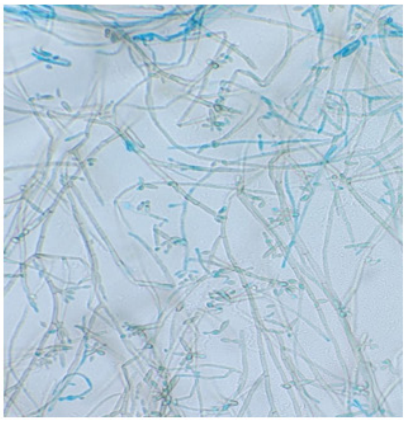

Figure 3: Microscopic studies in lactophenol cotton blue.

Second Case Report

A 54-year-old Omani female who had breast cancer who underwent surgery with no evidence of the disease later on. She had liver transplant 6 years back, kept on immunosuppression medication (Tacrolimus and prednisolone). She was admitted to the Department of Neurology, Khoula hospital, Oman, and presented with history of left sided weakness with history of fall from the bed and deterioration in the level of consciousness. The first computed tomography (CT) scan of the brain demonstrated single ring enhancing lesion with pus like material in center suggestive of abscess.

Full laboratory blood analysis revealed a hemoglobin level of 9.9 g/dl; white blood cells, serum electrolytes, and liver function test results were within normal ranges. Blood cultures were sterile. MRI brain suggestive of right frontal lobe ring-enhancing lesion associated with marked perilesional edema showing central restricted diffusion. The lesion most likely representing cerebral abscess, the possibility of metastatic lesion is less likely but cannot be rolled out keeping in view a case of breast cancer.

Neuosurgical intervention consisted of a right frontal craniotomy and excision of the mass. Intraoperative finding was small right frontal lesion with pus like material in the center. The material was analyzed by microbiological and histopathological laboratory.

Microscopic examination of the biopsy sections (pus tissue) stained with H&E stain (hematoxylin and eosin stain) revealed focal granulomatous inflammation and extensive necrosis. Abundant brown pigmented fungal conidia and fewer brown pigmented septate fungal hyphae is noted throughout the brain

parenchyma. The granulomas show multinucleated giant cells, some of which show pigmented septate branching fungal hyphae and conidia. The tentative diagnosis of CNS phaeohyphomycosis diagnosis was made. Patient started on liposomal amphotericin B and voriconazole.

The clinical specimen was cultured on sabouraud dextrose agar at 30 to 35°C. Growth of melanized fungi after 1 week was observed as dark brown colony with heaped center and flat edge. These fungi were morphologically classified as Fonsecaea pedrosoi. Figure 3

Microscopic studies using slides were prepared from these cultures in lactophenol cotton blue under biosafety level 3 regulations; showed brown one-celled conidia in short, branched chains. Figure 4

DNA was extracted, internal transcribed spacer (ITS) ribosomal DNA was amplified using primers and sequenced with the internal primers. PCR amplification and sequencing were performed and compared with entries in a molecular database. The isolate was identified as Fonsecaea pedrosoi.

The molecular results confirmed the mycological diagnosis, and histopathological observation led to the diagnosis of cerebral phaeohyphomycosis due to Fonsecaea pedrosoi.

For the management, the patient treated with both liposomal amphotericin B and voriconazole. Simultaneously, empirical antibacterial therapy, consisting of Meropenem and vancomycin was initiated. As there is no improvement, CT scan was repeated after 2 weeks showed new subdural abscess collection. Patient underwent another craniotomy for evacuation of the collection. Despite amphotericin B with voriconazole therapy and surgical management, the patient's condition continued to deteriorate, and he expired 3 weeks after diagnosis of the disease.

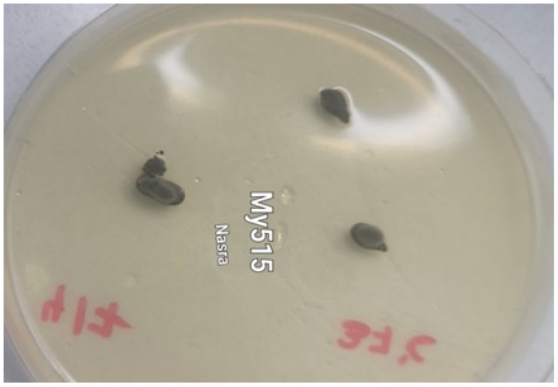

Figure 4: Fungal culture morphologically classified as *Fonsecaea pedrosoi.*

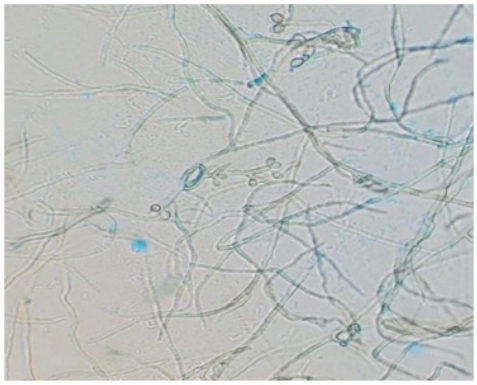

Figure 5: Microscopic studies in lactophenol cotton blue.

Discussion

Dematiaceous fungi, which contain melanin-like pigments in their cell walls, can lead to various infections in humans referred as phaeohyphomycosis (derived from the Greek word "phaeo," meaning "dark"). Among these infections, the most serious are those affecting the central nervous system. The melanin-like pigments in dematiaceous fungi give their hyphae a golden-brown appearance under a microscope, which can aid in diagnosis when examining histopathology samples. Since cultures are often not obtained, diagnosis typically relies on identifying pigmented fungal structures in histopathology samples. The classification of fungi causing cerebral phaeohyphomycosis has evolved, leading to confusion. Previously named Cladosporium trichoides, Xylohypha bantiana, and Cladosporium bantianum are now collectively recognized as Cladophialophora bantiana. Other fungi that cause cerebral phaeohyphomycosis include Wangiella dermatitidis, Dactylaria gallopava, Fonsecaea pedrosoi, Bipolaris spicifera, Rhinocladiella mackenziei, and species of Aureobasidium. The most common dematiaceous fungi causing cerebral phaeohyphomycosis are Cladophialophora bantiana, Wangiella dermatitidis, and Rhinocladiella mackenziei. Most individuals infected with R. mackenziei have been reported from Middle Eastern countries. However, cases have also been documented in other regions, including India, Afghanistan, and Pakistan [1-8].

Dematiaceous fungi can spread to the central nervous system through the paranasal sinuses by spore inhalation, especially in blocked sinus. As well it could disseminate through hematogenous pathway in patient with skin lesions, intravenous drugs user, and a heart-lung transplant recipient with pneumonitis [9-11].

The most clinical presentation in patient with cerebral phaeohyphomycosis with cerebral abseces are focal neurological deficit and seizures. Other symptoms like fever, headache, and sinusitis symptoms are less common. Head imaging usually show single enhancing lesion but in immunocompromised patients, it could represent as multiple lesions [12].

The diagnosis is typically confirmed through microscopic analysis of fluid aspirated from an abscess or tissue samples obtained during surgery. Histopathologic examination may show branching, septate hyphae, which often appear brown when stained with hematoxylin and eosin (H&E) or with potassium hydroxide (KOH). However, in some cases, the hyphae may lack pigment;

in such instances, specialized stains like the Fontana-Masson stain, which detects melanin, can be used.

The management of cerebral phaeohyphomycosis necessitates a combined approach involving surgical intervention and antifungal therapy. Complete surgical resection of the abscess is preferred over computed tomography (CT) guided aspiration, as it is associated with better outcomes. Antifungal therapy involves the use of amphotericin B and an azole, such as voriconazole, itraconazole, or posaconazole delayed-release tablets. The preferred regimen is Liposomal amphotericin B with voriconazole. Although, susceptibility testing for dematiaceous fungi has not been standardized, but studies indicated the above. Some isolates also show susceptibility to flucytosine, echinocandins, and terbinafine, though clinical evidence for these agents is limited. Antifungal therapy should be maintained for a minimum of six months, up to two years based on the case and clinical response [13, 14]

Despite advances in treatment, the prognosis for cerebral phaeohyphomycosis remains guarded, with survival rates of approximately 50% at two years, even with the availability of itraconazole and voriconazole [15].

There is a review of 101 documented cases worldwide, of culture-confirmed primary central nervous system (CNS) phaeohyphomycosis reported by one of the universities in Texas, between 1966 and 2002. They found that, the most commonly identified pathogen was Cladophialophora bantiana, followed by Ramichloridium mackenziei, which was exclusively observed in patients from the Middle East. Over half of the cases occurred in individuals without any known underlying immunocompromised state. Mortality rates remained elevated irrespective of the patient's immune status. Although there is no standardized therapeutic protocol, a combination of amphotericin B, flucytosine, and itraconazole has been associated with improved survival outcomes. Emerging azole antifungals, such as voriconazole, demonstrate broad-spectrum activity against these fungi; however, clinical data remain limited. Surgical intervention involving complete excision of brain lesions appears to yield superior outcomes compared to simple aspiration. An aggressive multimodal approach, combining medical and surgical strategies, is recommended to optimize treatment efficacy and patient prognosis in these infections [16].

Conflict of Interest Statement

None declared.

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