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Fonsecaea associated cerebral phaeohyphomycosis in a post-COVID-19 patient: A first case report

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ABSTRACT

Phaeohyphomycosis, previously known as chromoblastomycosis, is a chronic mycosis, usually affecting the skin. It is caused by dematiaceous fungi, which are a group of fungi that produce melanin in their cell walls. Cerebral phaeohyphomycosis occurs as a part of invasive presentation of the fungi, which usually affects immunocompromised patients, but may affect immunocompetent individuals as well. Cerebral infection in phaeohyphomycosis is associated with a poor prognosis regardless of the immune status of the patient. COVID-19 SARS-CoV-2 infection and/or medications used for its treatment may compromise the immune system, including in the post-COVID-19 period, resulting in invasive fungal infections, which have frequently been reported recently during the COVID-19 pandemic. We report a case of *Fonsecaea* associated cerebral phaeohyphomycosis in a recently diagnosed diabetic Omani lady, who presented to our hospital 6 weeks after recovery and discharge from hospitalization for moderate COVID-19 pneumonia.

Introduction

Cerebral fungal infections are relatively uncommon, and mostly affect immunocompromised patients. Only a few fungi are capable of causing disease in immunocompetent individuals (Davis, 1999). Most fungi live in the soil or on vegetation and infect humans only occasionally, by inhalation or through puncture wounds. Fungal infections usually reach the brain either by hematogenous route or by direct extension of infections from sinuses, ear canal or bone, or by direct inoculation secondary to cranial trauma or neurosurgical interventions (Chakrabarti, 2007).

Phaeohyphomycosis, previously known as chromoblastomycosis, is an infection caused by dematiaceous fungi, which are a group of fungi that produce melanin in their cell walls (Larone, 2011). Phaeohyphomycosis usually affect the skin, causing chronic mycosis. Cerebral phaeohyphomycosis occurs as a part of invasive presentation of the fungi, which usually affects immunocompromised patients, but may affect immunocompetent individual as well (Revankar et al., 2004). Cerebral infection in phaeohyphomycosis is associated with a poor prognosis regardless of the immune status of the patient (Revankar et al., 2004).

COVID-19 disease, caused by SARS-CoV-2 coronavirus, was declared a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020 by the World Health Organization (World Health Organization, 2005; World Health Organization, 2020) Since then the COVID-19 pandemic is still continuously evolving, and its associated pathophysiology and complications are continuously being discovered. Invasive fungal infections particularly Mucormycosis and Aspergillosis are not uncommon, generally or as a complication of COVID-19 infection and have been reported frequently during the COVID-19 pandemic (Soman and Sunavala, 2021; Manchanda et al., 2021). Invasive fungal infections caused by other fungi such as *Fonsecaea* are uncommon or rare. We report a case of *Fonsecaea* associated cerebral phaeohyphomycosis in a recently diagnosed diabetic Omani lady, who presented to our hospital 6 weeks after recovery and discharge from hospitalization for moderate COVID-19 pneumonia.

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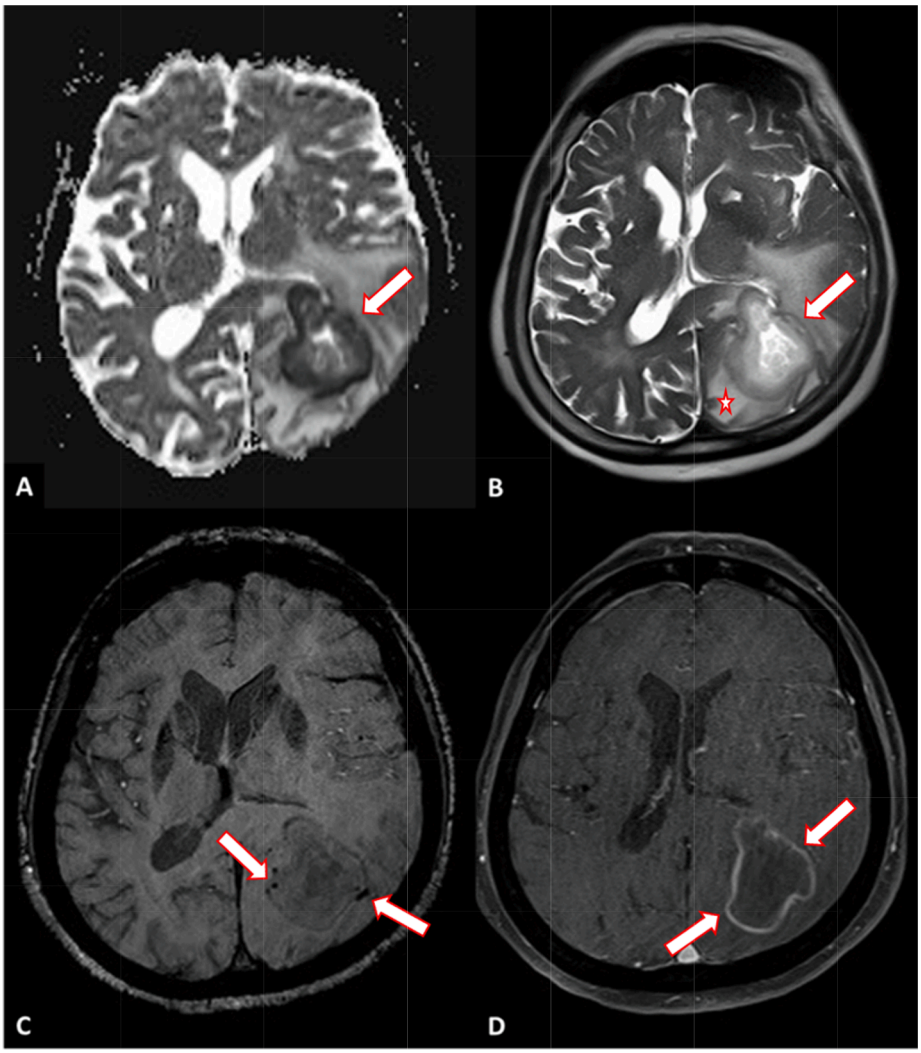


Fig. 1. MRI demonstrates left parieto-occipital space occupying lesion. On DWI not shown, the lesion is intensely bright peripherally with corresponding very dark signal on ADC map **(A)** (red-white arrow) consistent with significant diffusion restriction. On T2 **(B)**, the lesion demonstrates heterogenous signal intensity with hyperintensity centrally and intermediate signal peripherally with evidence of dark peripheral rim (red-white arrow) and surrounding vasogenic edema (red-white star). On SWI **(C)**, the lesion demonstrates foci of susceptibility artefacts peripherally denoting hemorrhage/ paramagnetic products such as iron/magnesium (red-white arrows). On Sagittal axial T1 post contrast **(D)** the lesion demonstrates smooth thin peripheral rim of enhancement (red-white arrows).

Clinical report

A 73-year-old Omani lady presented with 1-week history of occipital headache, unsteady gait and visual disturbance with blurred vision, and a 2-day history of confusion. She was known to have hypertension and was recently diagnosed with non-insulin dependent type-2 diabetes (6 months prior to presenting at our hospital). She was also diagnosed to have COVID-19 infection, 9 weeks prior to presentation at our hospital. She had no other known immunodeficiencies and testing for HIV-1 and HIV-2 antigens and antibodies was negative.

During her COVID-19 infection, she developed COVID-19 pneumonia, which was mild initially, and treated with oral antibiotics and steroids (dexamethasone 6 mg/OD) at home, but later the pneumonia became severe enough to require 4-day hospitalization and oxygen support via high flow nasal cannula. In-hospital, she received steroids (intravenous dexamethasone (6 mg/OD)) and antibiotic treatment (cefuroxime followed by ceftriaxone) for suspected superadded bacterial infection. Prior to admission for COVID-19 she was on oral hypoglycemics for control of her diabetes, but during her hospital stay, her blood glucose became uncontrolled, for which she required insulin injections. She was discharged from hospital on day-18 of COVID-19 infection, with a prescription for insulin for diabetes.

She then presented to our hospital 6 weeks after discharge for her COVID-19 pneumonia. On examination, she was confused, not oriented and Glasgow coma scale was 14/15 (E4M6V4). Motor examination was unremarkable and gait examination was difficult to assess due to her confusion. COVID-19 testing by PCR, on day of admission was negative. Her glycated hemoglobin (HbA1c) was 9.95% (reference range 4.4–6.4%). Brain imaging showed a rim enhancing lesion in the left parieto-occipital region with surrounding vasogenic edema (Fig. 1). The differential diagnoses of brain abscess and tumor were considered. She was given intravenous dexamethasone to reduce brain edema. She later underwent a left-parieto-occipital craniotomy and excision of lesion. The initial microscopic examination showed fungal hyphae on Gram stain. For histopathology examination the lesional tissue was fixed in 10% neutral buffered formalin, embedded in paraffin, serial sectioned at 5 μm, and stained with hematoxylin and eosin (H&E), Periodic acid-Schiff stain (PAS), and Grocott's methenamine silver stain (GMS) and the pathology revealed a brain abscess with mixed inflammatory cell infiltrate (consisting of neutrophils, lymphocytes, plasma cells and histiocytes), reactive astrocytes, and numerous pigmented brown septate branching fungal hyphae, best seen on H&E. A morphologic diagnosis of brain abscess with pigmented fungal organisms in keeping with cerebral phaeohyphomycosis was made (Fig. 2). Additional lesional tissue was submitted for fungal cultures. For the fungal cultures, the sample was inoculated onto Chocolate agar (Fig. 3 A) and Sabouraud dextrose agar (Fig. 3 B) plates. The plates were incubated at 30 °C and fungal growth was observed 1 week after incubation. The slow-growing colonies were greyish black in color, covered with a fine velvety mycelium, and produced a raised convex protrusion at the centers. Microscopically, smears made from the agar culture plates showed septate, loosely branching fungal hyphae with 'budding' growth of conidiophores and conidia

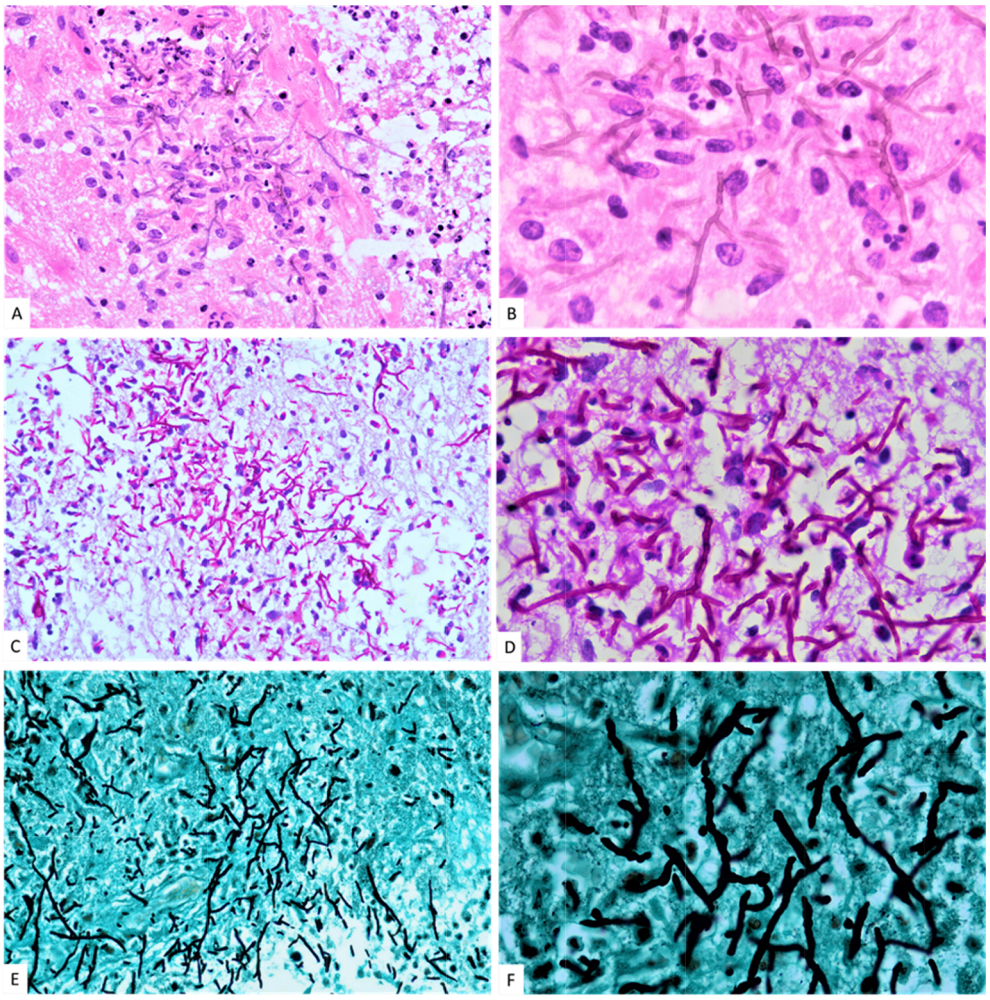


Fig. 2. Cerebral phaeohyphomycosis. (**A, B**) Brain abscess with mixed inflammatory cell infiltrate (consisting of neutrophils, lymphocytes, plasma cells and histiocytes), reactive astrocytes, and numerous pigmented brown septate branching fungal hyphae ((A) Hematoxylin & Eosin stain, magnification 40X, (B) Hematoxylin & Eosin stain, magnification 100X, oil). **(C, D, E, F)** Special stains highlight the numerous septate branching fungal hyphae (C) Periodic acid-Schiff (PAS) stain, magnification 40X, (D) Periodic acid-Schiff (PAS) stain, magnification 100X, oil, (E) Grocott's methenamine silver (GMS) stain, magnification 40X, (F) Grocott's methenamine silver (GMS) stain, magnification 100X, oil).

fruiting structure. The fungus was identified as *Fonsecaea species* based on morphology (Fig. 3 C, D). She was started empirically on liposomal amphotericin antifungal agent as well as ceftriaxone. Postoperatively, she did poorly, with declining level of consciousness and development of deranged liver enzymes. A second redo parieto-occipital craniotomy and excision drainage of abscess was done about 2 weeks after initial surgery, which revealed development of a superadded bacterial infection. She was initially given meropenem. Voriconazole was started in the following days, which was later switched to oral posaconazole suspension, due to side effects. Vancomycin was also added, but despite addition of new antibiotics, she kept deteriorating and developed sepsis with multiorgan failure, and blood culture grew *Enterococcus faecium*. She unfortunately had a cardiac arrest and passed away 6 weeks after admission. (Fig. 4 shows the complete timeline representing the clinical course of patients' COVID-19, COVID-19 pneumonia and *Fonsecaea* associated cerebral phaeohyphomycosis).

Discussion

Cerebral phaeohyphomycosis is a rare brain fungal infection that can affect immunocompetent and immunocompromised individuals (Revankar et al., 2004). It is caused by a wide variety of pigmented dematiaceous fungi, most common being *Cladophialophora bantiana*, *Rhinocladiella mackenziei* and *Exophiala dermatitidis* (Larone, 2011; Revankar et al., 2004; Garzoni et al., 2008; Brandt and Warnock, 2003).

Cerebral phaeohyphomycosis has variable central nervous system (CNS) manifestations, with brain abscess being the most classic clinical presentation (Revankar et al., 2004). Other manifestations include meningitis, encephalitis, myelitis and arachnoiditis (Revankar et al., 2004).

Fungi genus *Fonsecaea* is morphologically defined by the presence of melanized pigmented (dark/brown) septate, loosely branching hyphae, and pale brown or olivaceous conidia produced in short chains at the apex of the conidiophores (Larone, 2011). *Fonsecaea* is present worldwide, but it is more commonly prevalent in tropical and sub-tropical regions, and it is a saprobe, living on dead organic matter in the soil and rotting plant materials (Larone, 2011). Four species of *Fonsecaea* namely, *F. pedrosoi, F. monophora, F. nubica and F. pugnacius,* are currently recognized to cause disease in humans (Najafzadeh et al., 2009; Xi et al., 2009; de Azevedo et al., 2015; Costa et al., 2016; Bagla et al., 2016).

Our patient was relatively immunocompetent prior to getting COVID-19 infection. Her COVID-19 pneumonia was treated with steroids, and her diabetic glucose control worsened during the course of her COVID-19 infection. 6 weeks after her hospital discharge for COVID-19 pneumonia, she presented to our hospital with a brain abscess, which on histopathology showed a slow-growing fungus *Fonsecaea* associated cerebral phaeohyphomycosis. As COVID-19 pandemic is still underway, currently only fungal Mucormycosis and Aspergillosis infections have so far been reported affecting patients infected and recovering from COVID-19 (Soman and Sunavala, 2021; Manchanda et al., 2021). These patients have become immunocompromised due to different factors including the disease itself; exacerbation of existing chronic conditions such as diabetes mellitus during COVID-19 infection; and by using steroids and monoclonal antibody for treatment of COVID-19 (Pranata et al., 2021). COVID-19 infection is associated with development and

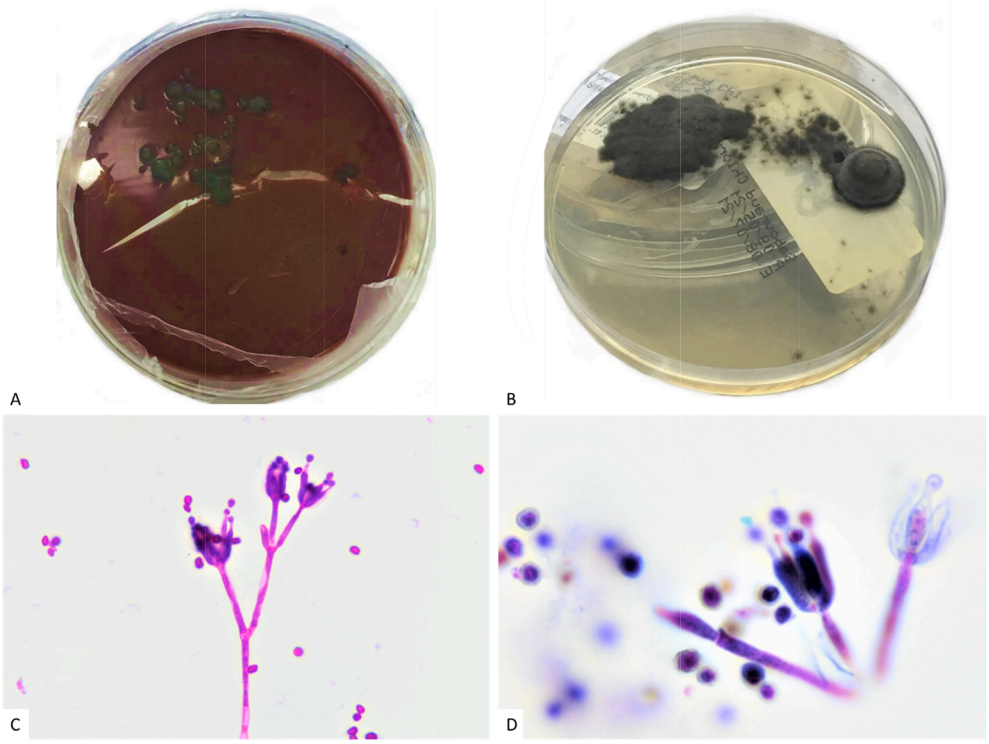
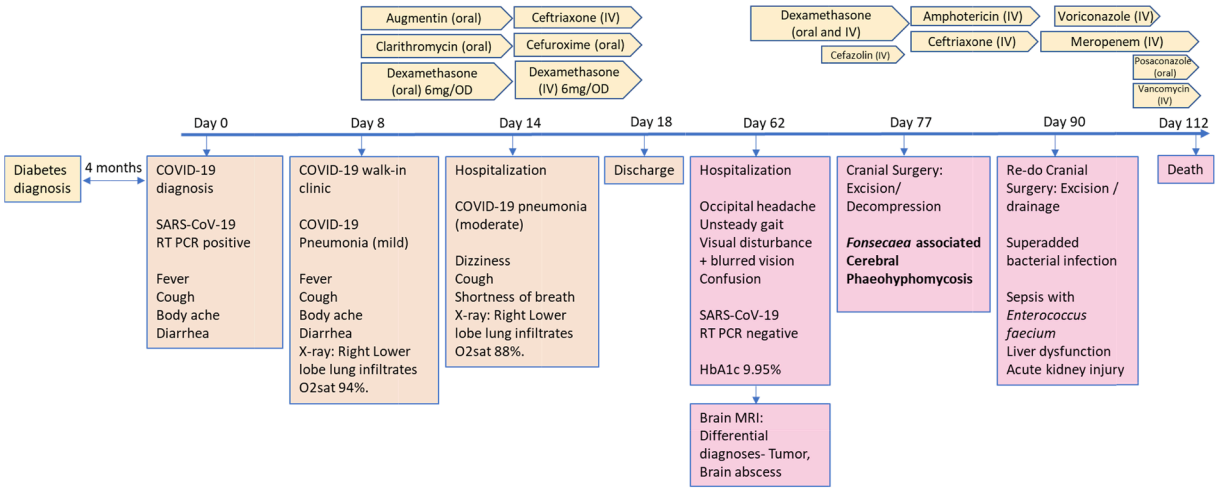


Fig. 3. **(A)** Chocolate agar and **(B)** Sabouraud dextrose agar plates showing greyish-black fungal colonies. **(C, D)** Microscopically, septate, loosely branching fungal hyphae with 'budding' growth of conidiophores and conidia fruiting structure were observed ((C) Periodic acid-Schiff stain, magnification 100X, oil, (D) Papanicolaou stain, magnification 100X, oil). The fungus was identified as *Fonsecaea.*



Timeline representing the course of patients' COVID-19, COVID-19 pneumonia and Cerebral Phaeohyphomycosis

Fig. 4. Complete timeline representing the clinical course of patients' COVID-19, COVID-19 pneumonia and *Fonsecaea* associated cerebral phaeohyphomycosis. (*HbA1c,* Glycated hemoglobin (reference range 4.4–6.4%).

exacerbation of diabetes mellitus as part of COVID-19 disease and post-COVID-19 syndrome (Pranata et al., 2021). In our case, we hypothesize that, the patients' treatment with steroids, and her exacerbation of diabetes during COVID-19 infection, lead her to be immunocompromised and more susceptible to fungal infections, and ours is the first reported case of a different fungal infection affecting a post-COVID-19 patient.

Conclusion

Fonsecaea associated cerebral phaeohyphomycosis is a serious fungal infection associated with high mortality. This is the first report worldwide, to our knowledge, that describes a case of *Fonsecaea* associated cerebral phaeohyphomycosis in a patient with recent COVID-19 infection. With the COVID-19 pandemic still continuously evolving, we should keep a low clinical threshold for invasive mould infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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