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A rare case of cerebral phaeohyphomycosis caused by *Fonsecaea* species in a renal transplant patient

Hammad Ul Haq Qureshi [a,1], Muhammad Absar [b,1,*], Wafa Nasser [c], Mohamed Tahar Yacoubi [b]

[a] Department of Neurosurgery, King Abdulaziz Hospital, Ministry of National Guard Health Affairs, AlAhsa, Saudi Arabia
[b] Department of Pathology and Laboratory Medicine, King Abdulaziz Hospital, Ministry of National Guard Health Affairs, AlAhsa, Saudi Arabia
[c] Infection Prevention & Control Program, Imam Abdulrahman Bin Faisal Hospital, Al-Dammam, Saudi Arabia

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ABSTRACT

Cerebral phaeohyphomycosis (CP) is a serious form of phaeohyphomycosis. We report a case of CP caused by *Fonsecaea* species in a 66-year-old immunocompromised renal transplant recipient female. Craniotomy was performed on an irregularly enhancing right cerebellar hemisphere lesion and abscess and tissue samples collected for microbiological and histological evaluation, showing fungal elements and *Fonsecaea* species was isolated. Antifungal treatment with voriconazole & liposomal amphotericin B was initiated with a temporary improvement in the patient's condition. Deep vein thrombosis jeopardized patient's prognosis. Despite aggressive surgical and medical intervention, our patient succumbed to the disease. Historically, CP has been linked with fatality rates as high as 65 %, despite surgical intervention and systemic antifungal medication.

1. Introduction

Cerebral infections by dematiaceous fungi are in general known as cerebral phaeohyphomycosis (CP). The term "dematiaceous fungi" refers to a group of fungi that are dark in color due to the presence of melanin in their cell walls. Melanin, although poorly understood, yet believed to be a virulence factor [1,2]. CP typically manifests as a single brain abscess that causes symptoms related to increased intracranial pressure, like headaches, seizures, or focal deficits [1,3]. Immunocompromised hosts are more likely to develop multiple brain abscesses. Due to extremely high rates of mortality from CP, an early diagnosis and proper surgical and medical interventions are essential for favorable outcome. The most accurate and probably frequently used approach of diagnosis involves identifying pigmented fungi from brain tissue histopathology or culture. The most effective course of treatment involves surgical resection and prompt administration of a combination of antifungal medications [4–6]. Many dematiaceous fungal species have been linked to CP, with *Cladophialophora bantiana* and *Rhinocladiella mackenziei* accounting for roughly 50 % and 15 % of CP cases, respectively [7,8]. Here we present a case of a CP caused by *Fonsecaea* species in a 66-year-old immunocompromised female who had received a kidney transplant.

2. Case presentation

A 66-year-old woman with a two-week history of headaches, dizziness, intermittent vomiting, and blurred vision presented to our emergency room (day 0). She had a three-year history of living-unrelated donor renal transplantation and was on prednisolone, mycophenolate mofetil, and tacrolimus. Upon evaluation, her Glasgow Coma Scale (GCS) score was 15/15. A preliminary non-contrast CT scan revealed a poorly defined hypo-density in the right cerebellar region. An urgent MRI examination revealed an irregularly enhancing lesion encompassing the right cerebellar hemisphere and measuring 26 × 53 × 55 mm, with some water restriction on diffusion images and surrounded by mild vasogenic edema. The fourth ventricle was affected by mass effect (Fig. 1a & b). Initial differential diagnoses included metastatic lesions, CNS lymphoma, and infectious lesions. On day +5, she underwent a right-sided posterior fossa craniotomy and debulking of this lesion in conjunction with the insertion of a right frontal external ventricular drain. We encountered a dense walled lesion with a necrotic core intraoperatively. Histology and microbiological analyses were performed on the biopsies. The cerebrospinal fluid was found to be clear. On tissue culture, *Klebsiella pneumoniae* was isolated and with infectious disease consultation, intravenous meningitic doses of meropenem along

* Corresponding author. King Abdulaziz Hospital, Ministry of National Guard Health Affairs, AlAhsa, Saudi Arabia.
E-mail address: ABSARMU@ngha.med.sa (M. Absar).
[1] Equal contribution.

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with vancomycin were commenced on day +7. Her EVD was removed five days after initial surgery (+day 10). The histopathology showed cerebellar abscess, lined by granulomatous reaction and centered by numerous faintly pigmented hyphae and spores (Fig. 2a & b), Grocott's methenamine silver (GMS) staining showed septate hyphae with spores (Fig. 2c), the fungal hyphae stained with Masson-Fontana stain (Fig. 2d). The KOH preparation was positive for pigmented hyphae. The fungus was slow growing and after 14 days, Sabouraud agar showed velvety, black fungal colonies. Fig. 2e shows colonies with convex, cone-shaped protrusions. To encourage sporulation and for further identification cornmeal agar was inoculated and microscopic features on lactophenol cotton blue (LPCB) showed stained septate, branching, brown hyphae as shown in Fig. 2f (LPCB, 400x). The microbiology and infectious disease teams, nephrology, radiology, histology, and the neurosurgery teams attended the multidisciplinary meeting. IV voriconazole (300mg twelve hourly) was added to the patient's treatment regimen on + day 12 and there were no side effects observed. It was also decided to withhold mycophenolate mofetil (one of the 3 immunosuppressive medications). The patient began to make remarkable clinical progress as her headaches and vomiting subsided. Prophylactic doses of unfractionated heparin were commenced subcutaneously to avoid any thromboembolic complication. She underwent insertion of a peripherally inserted central catheter (PICC) line for the administration of antibiotics and antifungal medication. Inflammatory indicators and clinical monitoring were conducted. The patient remained stable in the general ward, but her clinical condition deteriorated on + day 32 with worsening drowsiness (GCS 13–14/15) and headaches. A repeat MRI of the brain showed that the residual abscess collection was getting worse and that there was more mass effect. On day +33, she underwent another surgery (revision right posterior fossa craniotomy and reinsertion of EVD). On day +39, the histological investigations once again were positive for pigmented fungal elements. On day +47, fungal growth was observed, and a microscopic identification showed was *Fonsecaea* species. Once again, CSF culture was reported to have no growth. The EVD was removed six days post second surgery, and her GCS remained steady. Antibiotics/antifungals were given through an IV route, and on + day 40 liposomal amphotericin B (3mg/kg once daily) was added to voriconazole treatment regimen based on recommendations from local and regional infectious disease units. On day +44, despite prophylactic low molecular weight unfractionated heparin injections, the patient's course was complicated by severe bilateral lower limb deep vein thrombosis (DVT). After carefully weighing the risks and benefits and talking to all the teams involved and the patient's family, therapeutic heparin treatment was commenced. Her antibiotics and antifungals remained unchanged. On day +50, the patient experienced a significant worsening in GCS (4/15). On urgent CT, a significant posterior fossa bleeding with intraventricular extension was detected. Urgent EVD reinsertion was reperformed on the same day, and the patient was transferred to the ICU where she was sedated and mechanically ventilated. Her therapeutic heparin treatment was discontinued following this event. In the ICU, her GCS remained persistently low. On day +60, she suffered cardiac arrest and succumbed to death.

3. Discussion

Fonsecaea species belongs to the family Herpotrichiellaceae [9]. There are three species in the genus namely; *F. monophora, F. pedrosoi,* and *F. nubica*. *Fonsecaea* species are dematiaceous fungi. Classically, *Fonsecaea* spp. cause chromoblastomycosis. The fungus is found on plantation and other wooden objects mostly in tropical regions [10].

The *Fonsecaea* species CP epidemiology is not clear with cases reported from different parts of the world like Japan, Turkey, USA, UK, Iran, Brazil, India, and Saudi Arabia [11]. Previously, three cases of *Fonsecaea* species CP from Saudi Arabia in late 80s and early 90s were reported with deadly outcome [12,13]. We report, to the best of our knowledge, the first case (overall fourth case report) of *Fonsecaea* species cerebral infection from the Eastern region of Saudi Arabia. The mean age of onset of cerebral infection in the literature is 38 years (Supplemental Table 1), almost comparable with case reports summarized by Stokes et al., 2017 [14].

Fungal brain abcesses may appear like a tumor mass [4,15]. The imaging studies are usually non-specific and cannot distinguish between fungal and bacterial brain abscesses. Nevertheless, the accurate *Fonsecaea* species identification is only possible by molecular techniques. The initial surprising etiological clue of cerebral fungal infection is often made by the histopathology (also in this case). Microbiological isolation and identification of etiological agent is central for proper case management. These infections represent challenges to the clinicians due to paucity of literature and also lack of standard antifungal guidelines. Beside this, the pathophysiology of primary disease acquisition is not clear, possibilities includes seeding from fungal otitis media/sinusitis. Subclinical pulmonary infections leading to hematogenous spread is

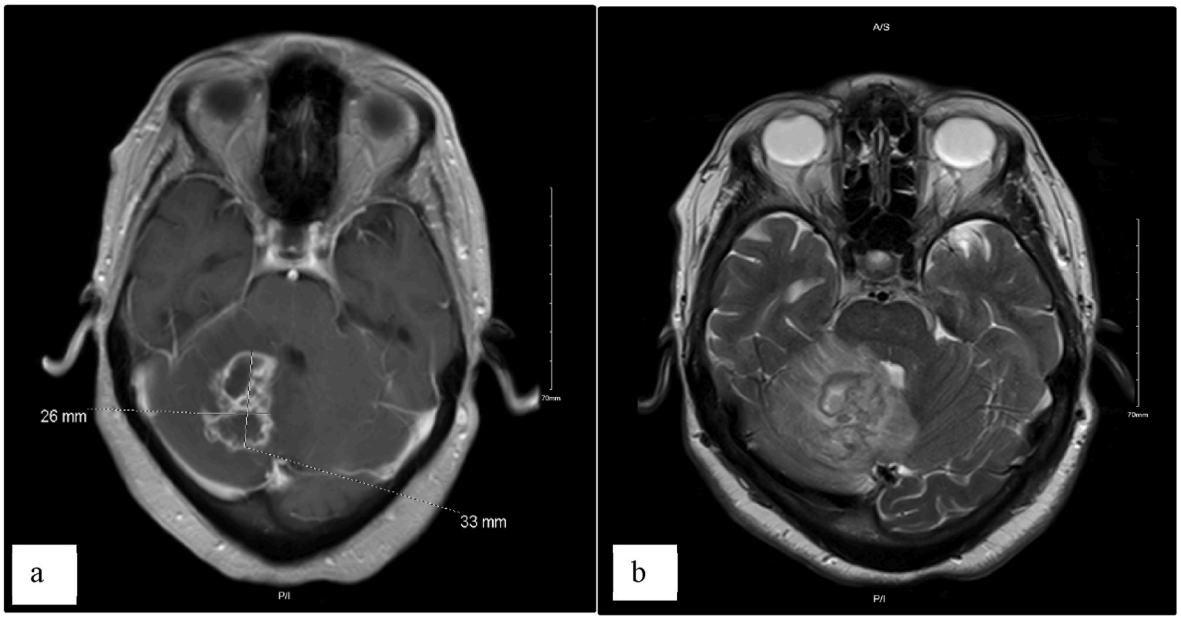

Fig. 1. Axial T1 **(a)** with contrast showing irregular enhancement of right cerebellar lesion. Axial T2 **(b)** weighted image showing surrounding vasogenic edema.

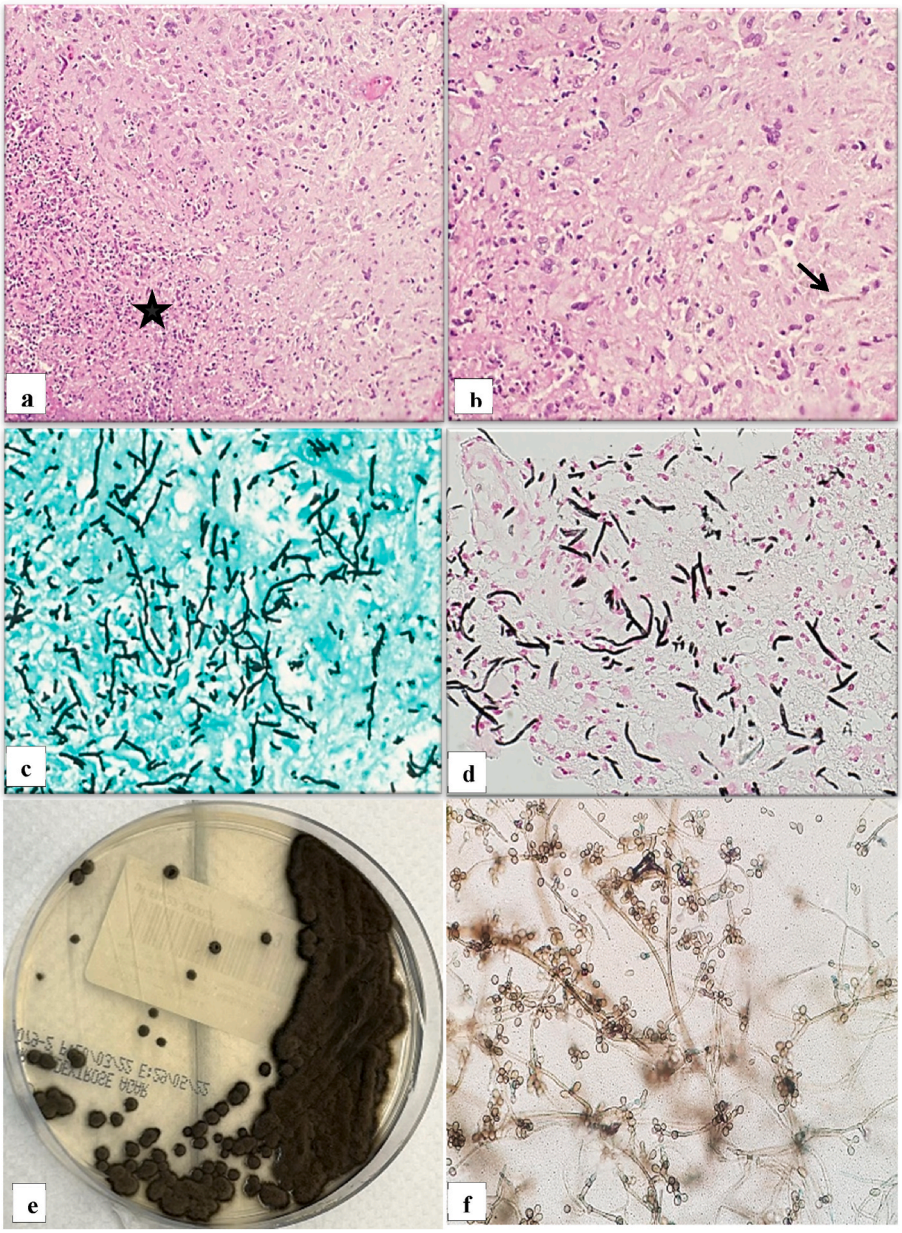

Fig. 2. Histopathological findings, (a+b): (HE staining x200, HE staining 400x), cerebellar abscess, lined by granulomatous reaction (star) and centered by numerous faintly pigmented hyphae and spores (arrow), (c) Grocott's methenamine silver (GMS) staining showed septate hyphae with spores, (d) the fungal hyphae stained with Masson-Fontana stain, (e) Culture on Sabouraud dextrose agar incubated at 30 °C showed the dark pigmented colonies of *Fonsecaea* species; (f) Microscopic view of branched, septate hyphae (brown in color) of *Fonsecaea* species, (LPCB, 400x).

considered the main culprit by most physician [4].

Fonsecaea pathogenesis involves many chemical compounds on the surface and secreted ones, e.g. melanin. Upregulation of cell wall adhesions occurs at temperatures ranging from 28 °C to 37 °C, enhancing the fungus' invasiveness [16]. *Fonsecaea* pedrosoi has been found in the cytoplasm of macrophages and epithelial cells, indicating its invasiveness [17]. Although none of the reviewed case reports mentions intracerebral bleeding as a complication, we are unsure of the cause of the intracerebral bleeding in the current case.

A literature review of CP case reports due to *Fonsecaea* species outlined a poor prognosis in vast majority of infections (Supplemental Table 1). The majority of reported cases in our literature search were diagnosed in immunocompetent individuals (84.6 %). The mortality rate was 59.1 % among the immunocompetent patients (13/22) vs. 50 % in immunocompromised patients (2 out of 4). The summary of antifungal minimum inhibitory concentrations (MIC), when reported, in the literature were as follows: amphotericin B (range: 0.25–4 μg/mL; itraconazole (range:0.03–0.5 μg/mL); voriconazole (range: 0.016–0.25 μg/mL); and posoconazole (range: <0.015–0.25 μg/mL).

The overall mortality rate was 57.8 % in 26 case reports (n = 15/26). The mortality rate was around 50 % in one study comprising 21 patients [18]; while reported mortality was high as 79 % in another study by Revankar et al., 2004 [8]. Due to its rarity and lack of clinical experience, *Fonsecaea* species treatment varies significantly among documented cases. Neurosurgery and treatment with voriconazole has shown a better prognosis [19]. In many cases, surgery and amphotericin B and an azole, or a blend of the two was prescribed for weeks to months. In one study, it was found that the overall mortality rate decreased (17 %) with combination therapy (amphotericin B, flucytosine, and itraconazole) relative to monotherapy (74 %) The limitation of this study was a small size and not evaluating the newer compounds like voriconazole and posoconazole [8]. Due to its high oral bioavailability and CNS

penetrance, voriconazole has shown improved outcomes [20]. To determine overall success, more research is necessary. Due to limited resources we were not able to test susceptibility to antifungals.

In conclusion, CP caused by *Fonsecaea* species is a serious infection with high fatality rate. Due to the infrequency of the infections, the most effective therapeutic strategy is unclear. This is the first case report of CP caused by *Fonsecaea* in Eastern Saudi Arabia. Our study contributes to the relatively limited literature and emphasizes the consideration of *Fonsecaea* species as a rare differential diagnosis for a cerebral tumor in immunocompromised patients.

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CRediT authorship contribution statement

Hammad Ul Haq Qureshi: Formal analysis, Data curation, Writing – original draft, collected and analyzed the data, and wrote the manuscript, read and approved the final version of the manuscript. **Muhammad Absar:** Formal analysis, Data curation, Writing – original draft, collected and analyzed the data, and wrote the manuscript, read and approved the final version of the manuscript. **Wafa Nasser:** Writing – review & editing, revised and edited the manuscript, read and approved the final version of the manuscript. **Mohamed Tahar Yacoubi:** Writing – review & editing, revised and edited the manuscript, read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest in this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mmcr.2023.100621.

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