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Case report

Cerebral and pulmonary phaeohyphomycosis due *Cladophialophora bantiana* in an immunocompromised patient

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ABSTRACT

We report a case of disseminated *Cladophialophora bantiana* phaeohyphomycosis with cerebral and pulmonary disease in a 69-year-old renal transplant recipient. The patient presented with confusion, low-grade fever and progressed quickly to a comatose state. Imaging revealed multiple small brain abscesses and a right pulmonary nodule. Cultures of bronchial washings and biopsy of the right pulmonary nodule grew *C. bantiana,* a highly neurotropic fungus with a high mortality rate. He was treated with Isavuconazonium sulfate (Isavuconazole) and Liposomal Amphotericin B along with reduction immunosuppressive therapy. His neurologic status remained unimproved despite treatment with dual antifungal therapy for two months. The patient eventually died from respiratory failure 79 days after his initial presentation, *C. bantiana* has been reported in both immunocompetent and immunocompromised patients. Its neurotropism has been reported and described in the literature with *C. bantiana* responsible for 50 % of the reported cases of fungal brain abscess. However, reports of pulmonary and cerebral involvement are exceedingly rare. Our patient was immunocompromised and succumbed to cerebral involvement.

Introduction

An identifying feature of all Dematiaceous fungi is their dark pigmentation attributed to melanin in their cell wall. They are distributed worldwide and generally found in soil or associated with plants. *Cladophialophora bantiana* is the most neurotropic of the dematiaceous fungi and has been associated with brain abscesses in both immunocompetent and immunocompromised hosts with higher mortalities reported in the latter group [1,2]. Here we report a case of disseminated phaeohyphomycosis due to *C. bantiana* in an immunocompromised renal transplant patient.

Case

A 69-year-old man transferred to our facility for continued management of dematiaceous fungal infection of the lung with presumed dissemination to the brain. The patient had a history of end stage renal disease (ESRD)for which he received a deceased donor renal transplant 3 years prior to presentation. Since his transplant, he had been maintained on Mycophenolate Mofetil 750 mg twice daily and Prednisone 10 mg daily for immunosuppression. He first presented to the initial hospital on 01/20/2020 with complaints of generalized malaise, cough, and confusion of one-month duration. A CT Chest (Image 1) revealed a 1.5 cm nodule in the posterior segment of his right upper lobe and multiple less than 5 mm soft tissue nodules scattered throughout the right lung and minimally in the left lung. Magnetic Resonance Imaging (MRI) of the brain (Image 2) showed multifocal bilateral supratentorial and bilateral subependymal and deep periventricular white matter irregularly shaped enhancing lesions concerning for brain abscess. CT guided right lung nodule biopsy demonstrated necrotic granulomatous inflammation with darkly pigmented organisms in hyphae form on Gomori Methanamine Stain (GMS), concerning for dematiaceous mold/phaeohyphomycosis. He was started on Voriconazole and Liposomal Amphotericin B (L-AmB) within one week of his initial presentation. His mental status continued to deteriorate throughout the hospital course, and he was then transferred to Augusta University Medical Center (AUMC) on 02/17/2020, 28 days after his initial presentation to an outside hospital. Infectious Disease was consulted and evaluated patient on same day of arrival. Patient was somnolent, minimally arousable with Glasgow Coma Scale of 6. He was promptly

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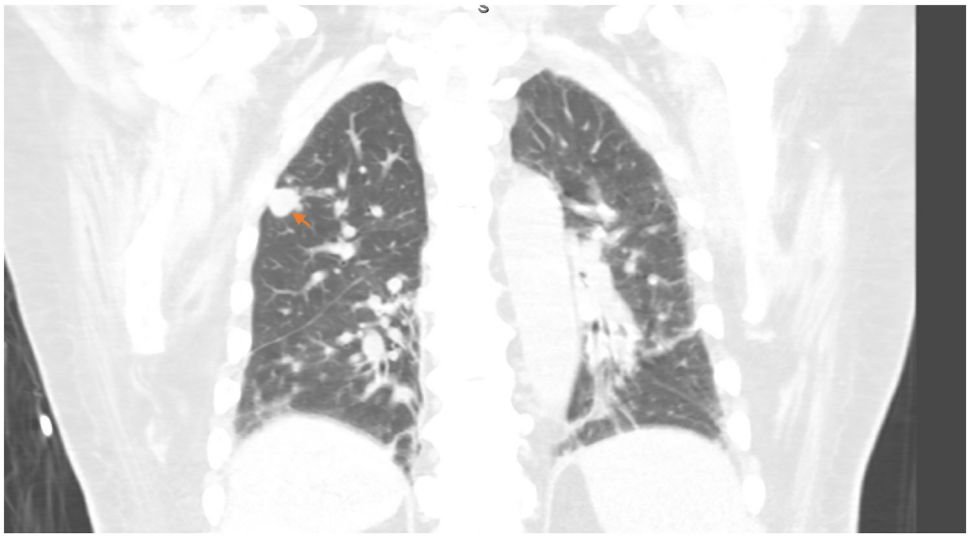

Image 1. CT scan of thorax without contrast, coronal view.
Numerous soft tissue density nodules throughout both lungs largest measuring 1.5x 1.3 cm in the periphery of the right upper lobe (orange arrow) and additional numerous sub-centimeter pulmonary nodules.

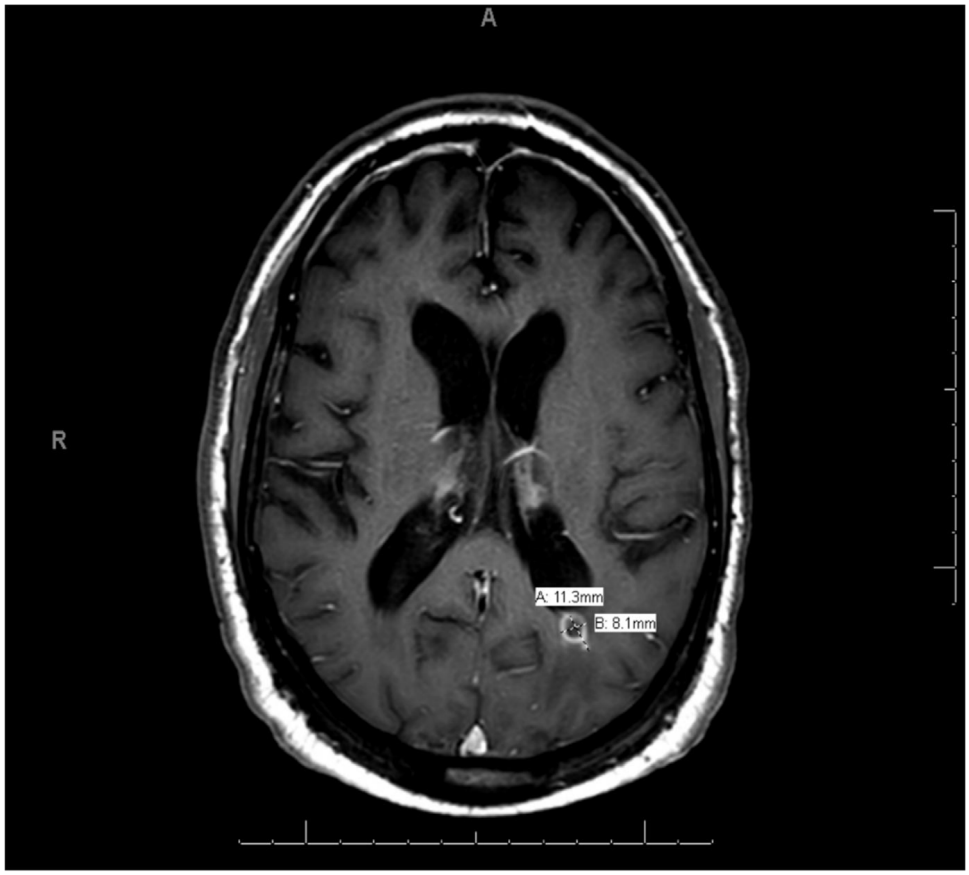

Image 2. MRI Brain performed at AUMC on 02/22/2020.
Compared with the MRI exam on 01/20/2020, This Axial view, T1Weighted image with contrast shows a Left parietal periventricular lesion along the posterior body of left lateral ventricle that is now demonstrating more cystic appearance with central diffusion restriction, likely small abscess measuring approximately 1.1 cm AP by 0.8 cm transverse, previously this measured approximately 1.2 × 0.9 cm.

intubated and bronchoalveolar lavage was done, bronchial washings and biopsy were sent for cultures. Repeat bronchoscopy was done on second day of admission at AUMC and lung biopsy obtained were also sent for cultures.

Using fluoroscopic guidance, lumbar puncture was performed on 02/18/2021 with opening pressure of 26 cmH_2O, analysis of Cerebrospinal fluid (CSF) obtained revealed elevated protein of 220 mg/dL, a normal glucose of 66 mg/dL, leukocytosis at 228 WBC/

mm^3, 55 % segmented cells, 29 % lymphocytes, 16 % monocytes and 5950 RBC/mm^3. CSF culture, gram stain, and cryptococcal antigen test were negative, brain biopsy showed neuroglial tissue with reactive astrocytes and microglia. Fungal cultures from bronchial washings grew *Cladophialophora bantiana.* Initial identification was after five days in culture, as a dematiaceous fungus, followed by species identification of *Cladophialophora* after 13 days in culture and final identification as *Cladophialophora (Xylohypha) bantiana* was obtained after 33 days in culture. This was consistent with the findings from a repeat right lung nodule biopsy taken at AUMC, the day after admission, that grew *Cladophialophora* species. After 7 days on admission at AUMC, Voriconazole was changed to Intravenous Isavuconazole for better side effect profile, mycophenolate mofetil was discontinued and Prednisone reduced to 5 mg daily on day 8, to minimize immune suppression and increase the chances of survival. He developed new persistent fevers on day 12 at AUMC, approximately five days after reducing immunosuppressant doses suggestive of abscess formation. Repeat MRI of the brain on day 19 at AUMC, demonstrated progression of current abscesses, new lesions and vasogenic edema shown in Image 2 . He underwent a tracheostomy on day 15 at AUMC and PEG tube placement on day 17. He remained stable on dual fungal therapy with Isavuconazole and L-AmB over the following 2 months. Despite the subsiding fever, his mental status remained poor with grimace only to pain. He was scheduled to be transferred to long term acute care hospital on Isavuconazole to be continued for at least 6 months with interval evaluation for clinical improvement. On day 51 at AUMC, the patient was pronounced dead due to respiratory failure, 79 days after his initial presentation at outside hospital.

Discussion

Cladophialophora Bantiana is a highly neurotropic dematiaceous fungi associated with high mortality even when antifungal treatments are administered. Although a rare disease, it is responsible for about 50 % of the reported cases of fungal brain abscess due to dematiaceous molds [1]. *C. bantiana* cerebral infections are associated with poor prognosis with a reported mortality rate of 65.0 % regardless of the individual's immune status [1]. Microscopic features of *C. bantiana* include hyaline-to-brown, septate hyphae arranged in long branched chains [3]. Melanin is a virulence factor for all the pigmented molds as it is thought to scavenge free radical, and hypochlorite produced by phagocytic cells in the oxidative burst thus preventing killing of the organism [4]. This feature, combined with a thermotolerance above 40 °C are considered two significant virulence factors that make it easier for this fungus to survive in brain tissue [5]. Treatment has been generally unsuccessful in most cases, this likely attributed to its virulence factors and poor penetration of the antifungal drugs through meninges and the abscesses wall [5].

The mode of central nervous system penetration of *C. bantiana* has yet to be clearly defined. As the lesions have been recorded in many parts of the brain with no known predilection for a particular region, it is likely that the agent possibly gains access through bloodstream from an innocuous site of infection in the lung or subcutaneous traumatic inoculation site which may be facilitated by immunosuppressive therapy [6].

The rarity and lack of specific symptoms and signs of the disease pose a significant barrier to obtaining early diagnosis. Imaging modalities such as CT or MRI do not show findings specific to *C. bantiana* and lesions may appear similar to bacterial or tuberculous abscess [7]. Therefore, a specimen sample, direct microscopy and culture are considered essential for diagnosis [1].

Cases in which *C. bantiana* presents with both lung and cerebral involvement are extremely rare and certainly more complicated to treat. In a recent systematic review of 120 case reports, lung infection along with cerebral involvement was documented only in three of the 120 cases [5]. Although the data on therapeutics and prognosis is limited, no single antifungal or combination of antifungals has proven to be effective. Surgical resection in combination with utilization of antifungals with good CSF penetration were associated with better survival [8–11]. In this case, the patients' multiple small abscesses excluded the feasibility of surgical intervention and he received medical treatment alone. Further investigations into the *in vivo* antifungal susceptibility of the strain of *C. bantiana* would be of great value to developing future therapeutic recommendations.

Declaration of Competing Interest

The authors report no declarations of interest.

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Consent

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Authors contribution

Claudia Hernandez – case report design, data collection, writing.

Folake Lawal – case report design, review, edit, proofread.

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