



Case Report

Acrophialophora levis brain abscess in a kidney transplant patient: A case report and review of the literature

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ABSTRACT

We report the first case of *Acrophialophora levis* causing cerebral phaeohiphomycosis in a solid organ transplantation recipient. *A. levis* is a rare cause of invasive dematiaceous fungal infection among immunocompromised persons. We describe the clinical course of a kidney transplant patient who presented with acute hemiplegia due to a brain abscess from which *A. levis* was isolated. We review published clinical cases attributed to *Acrophialophora* species infection and discuss current limitations in its identification, diagnosis and management.

1. Introduction

The *Acrophialophora* genus are thermotolerant fungi found in the soil of temperate and tropical regions [1]. There are now three recognized species: *A. fusispora*, *A. levis*, *A. nainiana*. Earlier reports of *Acrophialophora* classified all as *A. fusispora* based on morphology [2]. However, a recent sequencing analysis of *Acrophialophora* isolates found that while the three species are 99.9% homologous in large subunit ribosomal DNA, differences in internal transcribed spacer (ITS) and β -tubulin allow for species-level discrimination [3]. *Acrophialophora* form white colonies on culture media that age to grey/brown with a “black reverse.” This distinguishing feature of dematiaceous, or pigmented, molds is attributed to melanin-laden cell walls [1].

Dematiaceous molds are considered opportunistic pathogens and therefore rare entities of clinical disease. However, their epidemiology is evolving in the era of transplantation medicine and use of immunosuppressants for autoimmune and other conditions. Among a growing population of chronically immunocompromised patients, the prevalence of dematiaceous fungal infections, globally termed “phaeohiphomycosis,” is increasing [4]. Clinical illness ranges from mild superficial to life-threatening disseminated infection depending on host immunocompetency.

Cerebral phaeohiphomycosis is particularly devastating with mortality rates as high as 70–80% [5]. The route of intracranial infection is presumed to be either direct extension from the paranasal sinuses or hematogenous with an initial, usually subclinical, pulmonary focus.

Previous reports speculate that some dematiaceous molds, including *Acrophialophora*, exhibit neurotropism [2] facilitated by melanin in the cell wall as a selective virulence factor [6]. The classic constellation of symptoms (i.e. fever, headache, focal neurologic deficits) is often absent among immunocompromised hosts, possibly leading to delayed diagnosis. Other potential contributors to poor clinical outcomes in patients with cerebral phaeohiphomycosis include: (1) difficulty in intracranial sampling to arrive at a tissue diagnosis, (2) limited diagnostics for mold identification, and (3) lack of adequate antifungal susceptibility data to guide appropriate treatment plans.

2. Case

A 54-year-old female with hypertension and type 2 diabetes complicated by end-stage renal disease prompting deceased-donor kidney transplantation on day –269 was admitted for acute right hemiparesis on hospital day 0.

The patient's immediate post-transplant course was complicated by acute cellular rejection on day –263 requiring thymoglobulin with return of graft function. On day –24 she was hospitalized for significant proteinuria due to *de novo* collapsing focal segmental glomerulosclerosis for which she received high-dose steroids and plasmapheresis. She was treated for *Candida* esophagitis with fluconazole loading dose 400mg PO followed by renally-dosed 100mg PO daily for 14 days and cytomegalovirus viremia with valganciclovir 450mg PO daily. She was maintained on immunosuppressive therapy with

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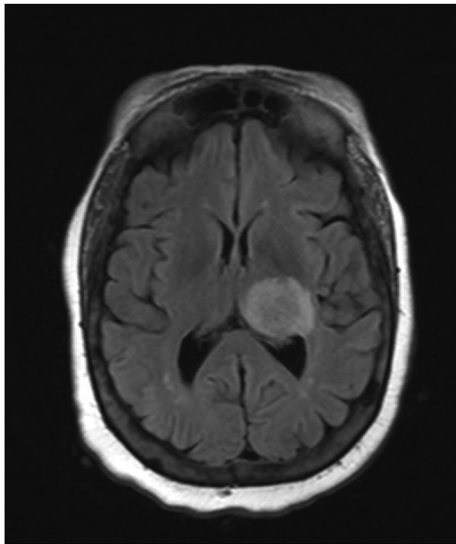


Fig. 1. Magnetic resonance imaging of the brain revealing a ring-enhancing lesion in the left thalamus [1.9×2.2 cm], consistent with early abscess formation, accompanied by peripherally scattered infarcts in the left cerebral hemisphere and cerebellum on T2 sequencing.

mycophenolate 500mg PO BID, tacrolimus 1mg PO qAM and 2mg PO qPM and prednisone 5mg PO daily.

This admission she presented with 8 h of right-sided weakness and was found to have right facial droop and 2/5 strength in her right upper and lower extremities. The remainder of her neurologic exam was intact, including mentation, speech, reflexes, sensation and proprioception. The patient lived with her two adult children in an urban setting. She did not smoke tobacco, drink alcohol or use illicit drugs. She did not spend significant time outdoors and had no recent travel or sick contacts.

Laboratory studies were notable for neutropenia (absolute neutrophil count 540 cells/mcL) and post-transplant renal insufficiency unchanged from her recent baseline (creatinine 2.0 mg/dL). Chest radiograph did not show evidence of cardiopulmonary disease. A non-contrasted computerized tomography scan of the head revealed a left thalamic hypodensity (1.9×2.2 cm) with local mass effect. Brain magnetic resonance imaging further characterized the lesion as ring-enhancing on T2 sequencing, highly concerning for early abscess formation (Fig. 1). She was started empirically on vancomycin and meropenem, and underwent lumbar puncture (opening pressure normal at 10 cm H₂O) on day +1. Cerebrospinal fluid (CSF) assessment revealed one nucleated cell with elevated glucose (116 mg/dL) and protein (141 mg/dL). Additional CSF evaluation was unrevealing, including bacterial, acid-fast bacilli and fungal cultures; Cryptococcal antigen; polymerase chain reaction testing for *Toxoplasma gondii*, Epstein-Barr virus, cytomegalovirus, *Mycobacterium tuberculosis* complex.

Stereotactic biopsy of the thalamic brain lesion on day +3 aspirated frank purulence. This specimen grew downy, white colonies on blood agar and Sabouraud dextrose media within 48 hours of being plated (Fig. 2). Subsequently, antibacterials were discontinued and voriconazole 6mg/kg IV BID for two doses followed by 4 mg/kg IV BID was initiated on day +5 given concern for an invasive mold infection. Microscopy showed pigmented hyphae with short phialides with swollen bases and cylindrical conidia in short chains (Fig. 3). Multiple attempts at identifying the organism by matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-ToF MS) were unsuccessful. The isolate was sent to the Centers for Disease Control and Prevention (CDC) whereby DNA sequencing of the ITS and β -tubulin identified *Acrophialophora levis* on day +14. Antifungal susceptibility testing of the isolate by the CDC were available on day +21 and

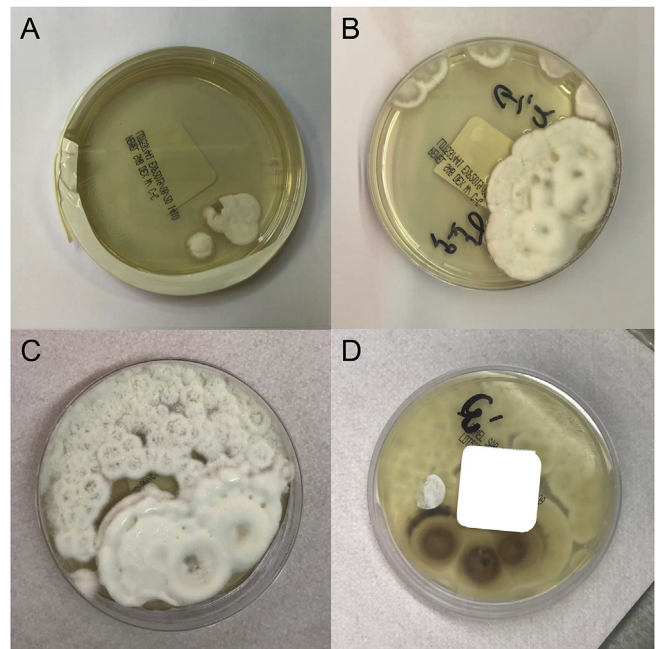


Fig. 2. Left thalamic brain tissue plated on Sabouraud dextrose media demonstrating the progression of colony growth from day +6 (A) to day +16 (B) to day +23 (C obverse, D reverse); the latter depicting the characteristic “black reverse” of dematiaceous fungi. The isolate was identified as *Acrophialophora levis* by internal transcribed spacer and β -tubulin DNA sequencing performed by the Centers for Disease Control and Prevention (CDC).

revealed the following minimum inhibitory concentration (MIC) values: voriconazole 0.25 μ g/mL, fluconazole 8 μ g/mL, itraconazole 0.06 μ g/mL, posaconazole 0.06 μ g/mL, isavuconazole 0.25 μ g/mL, anidulafungin 0.5 μ g/mL, caspofungin 1 μ g/mL, micafungin 1 μ g/mL (by broth microdilution read at 48 hours) and amphotericin 1.5 μ g/mL (determined using Etest following 48 hours of growth). MIC values for quality control isolates were in range.

The patient experienced encephalopathy following the brain biopsy which prolonged her clinical recovery. With continued therapy that was transitioned to voriconazole 300mg PO BID, her mental status returned to baseline, however, her right-sided weakness persisted. She was transferred to a subacute rehabilitation facility for continued care on hospital day +32. Serum voriconazole level was checked on day +121 and returned therapeutic at 5.6 mcg/mL (range 1.0–6.0 mcg/mL).

3. Discussion

Our patient experience is the first to our knowledge reporting isolation of *A. levis* from a clinical specimen. There have been nine previously published clinical cases of *Acrophialophora* species infection, all attributed to *A. fusispora* (Table 1). Cases included keratitis [7–10], pulmonary infection (two of which occurred in lung transplantation recipients) [11], and brain abscesses [2,12]. It is likely that *A. levis* as an etiologic agent of clinical disease has been previously underrecognized and underreported. A sequencing analysis of 39 *Acrophialophora* isolates (32 from human clinical specimens; 7 from environmental/animal sources) identified 73% of isolates initially considered *A. fusispora* as *A. levis* [3]. All isolates reclassified as *A. levis*, except one, were derived from human specimens, suggesting this species may be the most common *Acrophialophora* causing clinical disease. Only 16% (5/32) of the clinical isolates were linked to accession numbers published in case reports, implying the incidence of human disease secondary to *Acrophialophora* far exceeds the number of reported cases and that the majority may be due to *A. levis*.

Challenges with accurate mold identification likely also contributes

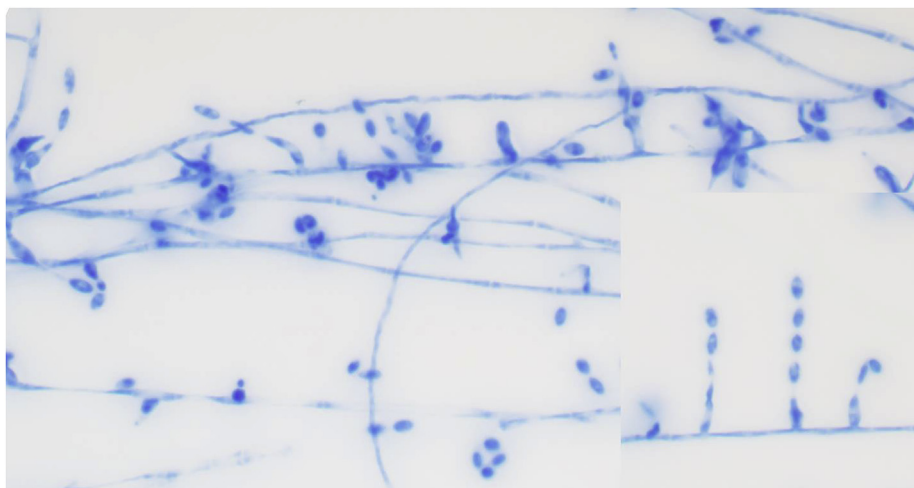


Fig. 3. Biopsy of left thalamic brain tissue stained with lactophenol cotton blue shown under microscopy 40x power revealing unbranched pigmented hyphae with short phialides with swollen bases and cylindrical conidia in short chains (inset) suggestive of cerebral phaeohyphomycosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

to limited reports of *Acrophialophora* as an agent of clinically relevant disease. *Acrophialophora* has been misidentified as *Scopulariopsis chartarum* [13] and *Scedosporium prolificans* [9], the latter being the most common cause of disseminated phaeohyphomycosis [14]. Further, a case of *Acrophialophora* cultured from bronchial secretions of a lung transplantation recipient highlights underappreciation of this organism as a true pathogen [7]. The result was assumed to represent contamination, antifungal therapy was discontinued, and unfortunately, the patient died 50 days later. On autopsy, *Acrophialophora* was isolated from lung tissue with evidence of pulmonary dissemination. Taken together, *Acrophialophora* may be more commonly implicated as an opportunistic infection than previously acknowledged, and under-recognition can lead to poor clinical outcomes.

Given morphologic similarity between *Acrophialophora* species by microscopy, more sensitive methods of identification are needed for species differentiation. While use of MALDI-ToF MS has been widely adopted in microbiology laboratories in the U.S. and Europe for rapid bacterial and yeast biotyping, its utility for mold identification is less well-established. Several genera commonly implicated in human disease (including *Aspergillus*, *Fusarium*, *Penicillium*, and *Trichoderma*) have been successfully identified by MALDI-ToF MS [15], however, an identification will not be returned when there is no reference spectrum available in the database, as was the case for our patient. Ten days lapsed between initial colony growth on culture media to identification of *A. levis* by DNA sequencing of the isolate performed by the CDC. Given that fungal sequencing is not routinely available in clinical microbiology laboratories, expansion of the MALDI-ToF MS reference library to include a wider array of dematiaceous molds would facilitate more rapid and accurate detection of these emerging clinical pathogens.

Optimal treatment for *Acrophialophora* and other neurotropic molds is not clearly established. Further, susceptibility testing of dematiaceous fungi has not been standardized. A consensus approach to managing

cerebral phaeohyphomycosis (based on published cases) is surgical resection of the abscess and combination antifungal therapy, typically with liposomal amphotericin B and an azole. For example, a case of acute lymphoblastic leukemia complicated by brain and pulmonary abscesses secondary to *Acrophialophora* did not improve clinically after 26 days of amphotericin B until itraconazole was added [2]. While itraconazole has sufficient brain tissue penetration, its low activity in the CSF may risk inadequate treatment of phaeohyphomycotic meningitis. Therefore, voriconazole is a particularly good candidate for empiric coverage given its excellent penetration into both brain tissue and CSF [5]. Successful treatment of *Acrophialophora* is challenging, with several reported fatalities despite receipt of appropriate azole therapy [7,12]. Further investigation of optimal management is needed.

4. Conclusions

We report the first case of *Acrophialophora levis* causing cerebral phaeohyphomycosis in a kidney transplantation recipient. Identification by ITS and β -tubulin DNA sequencing after failing to identify on MALDI-ToF MS allowed for accurate discrimination between closely-related *Acrophialophora* species and rapid initiation of appropriate therapy with voriconazole. With the increasing use of immunosuppressive agents, especially in the context of transplantation medicine, dedicated surveillance of this pathogen is needed to better characterize its evolving epidemiology. Finally, a high level of clinical suspicion for neurotropic dematiaceous fungi, including *Acrophialophora*, must be employed when considering the different etiologies of a brain abscess in an immunocompromised host, as delayed diagnosis and treatment initiation is likely to be fatal.

Table 1

Summary of nine clinical cases of *Acrophialophora* species published to date in the literature.

Case	Year	Location	Age	Sex	Risk Factor	Site of Positive Culture	Species Identified	Antifungals	Outcome	Reference
1	2000	Saudi Arabia	12	F	acute lymphoblastic leukemia	brain	<i>A. fusispora</i>	amphotericin B + itraconazole	survived	[2]
2	2001	United States	76	F	keratitis (contact lens)	eye	<i>A. fusispora</i>	itraconazole	survived	[11]
3	2001	Taiwan	60	M	HIV/AIDS	brain	<i>A. fusispora</i>	voriconazole	died	[15]
4	2004	France	13	M	cystic fibrosis	BAL	<i>A. fusispora</i>	itraconazole	survived	[14]
5	2004	France	26	F	cystic fibrosis	BAL	<i>A. fusispora</i>	itraconazole	survived	[14]
6	2007	India	55	F	traumatic keratitis	eye	<i>A. fusispora</i>	fluconazole	LTFU	[10]
7	2007	Portugal	33	M	bilateral lung transplant	BAL	<i>A. fusispora</i>	voriconazole	survived	[10]
8	2007	Spain	67	M	single lung transplant	sputum	<i>A. fusispora</i>	amphotericin B + itraconazole	died	[10]
9	2017	Japan	77	M	neutropenia, prostate cancer	eye	<i>Acrophialophora</i> sp.	voriconazole	survived	[12]

Abbreviations: BAL = bronchoalveolar lavage; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; LTFU = lost to follow-up.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Declaration of competing interest

There are no conflicts of interest among any of the authors.

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