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Meningitis Caused by *Candida Dubliniensis* in a Patient with Cirrhosis: A Case Report and Review of the Literature

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Abstract *Candida* species, including *Candida dubliniensis*, are a rare cause of meningitis. Herein, we report the second case of *C. dubliniensis* meningitis in a 49-year-old man with a history of hepatitis C virus-related cirrhosis, substance use disorder, and recent exposure to intravenous antibiotic therapy, presenting with confusion, abnormal gait, and urinary incontinence. Magnetic resonance imaging (MRI) of the brain showed marked hydrocephalus and leptomeningeal enhancement. Initial cerebrospinal fluid (CSF) studies were concerning for bacterial meningitis, although cultures were negative. Despite empiric treatment with broad-spectrum antibiotics, the patient's mental status declined. The diagnosis of *C. dubliniensis* meningitis was not made until the third lumbar puncture. The patient was treated with liposomal amphotericin B and flucytosine. Despite improvement of hydrocephalus on MRI of the brain and sterilization of CSF, the patient's mental status declined and he expired. This case highlights the difficulty in the diagnosis of *C. dubliniensis* meningitis as multiple lumbar punctures may be necessary. *C. dubliniensis* meningitis should be considered in the differential diagnosis for a patient with risk factors such as end-stage liver disease, human immunodeficiency virus infection, recent chemotherapy, substance use disorders, and recent broad-spectrum antibiotic use. A high index of suspicion is necessary as delay in initiation of therapy is associated with high mortality. The optimal treatment strategy has not been determined.

Keywords *Candida dubliniensis* · Meningitis · Hydrocephalus · Cirrhosis · Fungal meningitis

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Introduction

Candida dubliniensis was first discovered in the oropharynx of human immunodeficiency virus (HIV)-infected patients in Dublin, Ireland [1]. *C. dubliniensis* is phenotypically similar to *Candida albicans* as both are the only *Candida* species that can produce hyphae and chlamydospores [2]. They both form germ tubes in serum [3]. Phenotypically, they differ as *C. albicans* can grow at 42–45 °C,

whereas *C. dubliniensis* cannot. *C. albicans* is thought to be a more pathogenic organism based on its ability to tolerate thermal and oxidative stress. In addition, *C. dubliniensis* is missing important virulence genes possessed by *C. albicans* [2].

Candida meningitis is exceedingly rare and is usually caused by *C. albicans* [4–6]. It typically occurs in neonates or after neurosurgical procedures [6]. Occasionally, a delayed presentation of *C. albicans* meningitis has been observed in the setting of candidemia [7, 8]. The proposed pathophysiology is hematogenous seeding of the cerebrospinal fluid (CSF) that remains dormant until an iatrogenic intervention, such as steroid or broad-spectrum antibiotic use, unmasks the fungal infection [7]. If left untreated, *Candida* meningitis has a mortality rate of 57 % [4]. To date, there has been only one reported case of *C. dubliniensis* meningitis [9]. We present the second case with similar features to the first case, but unfortunately with a fatal outcome.

Case Presentation

A 60-year-old man presented with one week of progressive confusion, unsteady gait, and urinary incontinence. His past medical history was notable for compensated hepatitis C virus (HCV)-related cirrhosis, insulin-dependent diabetes mellitus, and substance use disorder in remission on methadone.

Three months prior to admission, the patient had been diagnosed with right leg cellulitis and treated with a 2-week course of intravenous (IV) and oral broad-spectrum antibiotics. Two months prior to admission, he was diagnosed with osteomyelitis of his toe and was treated with 6 weeks of IV broad-spectrum antibiotics through a peripherally inserted central catheter.

One week prior to admission, the patient was noted to have increasing confusion. On admission, he was afebrile. He was drowsy but oriented to person and was able to follow simple commands. He had no nuchal rigidity, photophobia, or focal neurological symptoms. Laboratory studies were unremarkable. HIV antibody test and serum cryptococcal antigen were negative. Urine toxicology was positive for methadone. Ammonia level was within normal limits. Blood alcohol level was negative.

Magnetic resonance imaging (MRI) of the brain showed marked non-obstructing hydrocephalus (Fig. 1), and diffusion-weighted imaging suggested exudative debris in the lateral ventricles.

Initial lumbar puncture showed high opening pressure, 1160 white blood cell (WBC)/high-power field (hpf) with granulocyte predominance, glucose 35 mg/dL and protein 430 mg/dL (Table 1). Gram stain showed no organisms. Initial bacterial, fungal, and acid-fast cultures were negative.

The patient was started empirically on IV vancomycin, ceftriaxone, ampicillin, and acyclovir. Serial lumbar punctures were performed to relieve high opening pressures. Additional studies included negative serum cysticercosis IgG, *Borrelia burgdorferi* IgG, *Listeria monocytogenes* IgG, *Entamoeba histolytica* IgG, *Coccidioides immitis* IgG, West Nile virus (WNV) IgM, Venereal Disease Research Laboratory (VDRL), and cryptococcal antigen. Polymerase chain reaction (PCR) testing for toxoplasmosis, herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus, Epstein–Barr virus, enterovirus, human parechovirus, human herpesvirus 6, and adenovirus was all negative, as were acid-fast stain and culture. Paraneoplastic antibody evaluation was negative. Transesophageal echocardiogram showed no evidence of endocarditis. Electroencephalography was negative for seizures.

On hospital day seven, the patient was arousable only to touch. A third lumbar puncture showed worsening leukocytosis and persistent elevated protein (Table 1). Gram stain revealed one yeast per hpf, and fungal culture grew *C. dubliniensis.* The identification was made using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) (Vitek MS) with the FDA-cleared in vitro diagnostics (IVD) database with a match of 99.9 %. The identity of *C. dubliniensis* was confirmed through the use of the MicroSeq D2 LSU rDNA Fungal Identification System (Applied Biosystems). The generated sequence was entered into the Basic Local Alignment Search Tool (BLAST), and 100 % identity was seen to three *C. dubliniensis* type strains (GenBank accession #KU948549). The next closest match was 96 % to type strains of *C. albicans*, allowing a species level identification of *C. dubliniensis* according to accepted criteria [10]. Susceptibility testing was done using the VITEK 2 yeast antifungal susceptibility testing (AST) card (BioMérieux SA (2010) VITEK 2

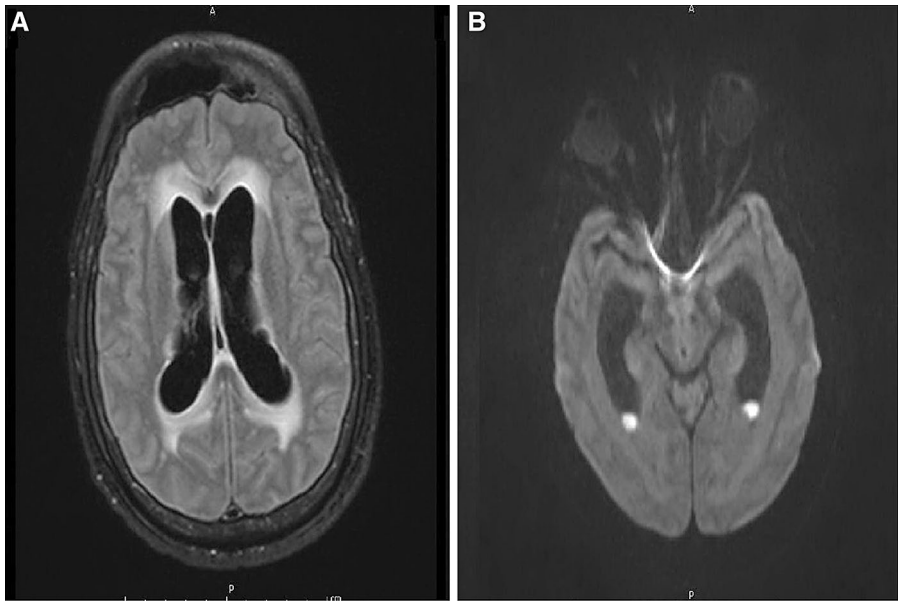

Fig. 1 MRI of the brain showing: **a** fluid-attenuated inversion recovery (FLAIR) sequence; periventricular hyperintensity consistent with transependymal flow concerning for hydrocephalus. **b** Diffusion-weighted imaging (DWI) sequence; foci of restricted diffusion layering in occipital horns (also seen in fourth ventricle, not shown) concerning for exudative debris or pus and ventriculitis or ependymitis

Table 1 Cerebrospinal fluid (CSF) studies in a patient with *Candida dubliniensis* meningitis before (−) and during (+) antifungal therapy

Days from initiation of antifungal therapy					
	−6	−3	0	+1	+22
Nucleated cells/uL	1160	800	2310	720	100
Glucose mg/dL	35	70	55	35	45
Protein mg/dL	430	410	450	560	320
Gram stain	Negative	Negative	1 + yeast	Negative	Negative
Culture	Negative	Negative	1 + *C. dubliniensis*	1 + *C. dubliniensis*	Negative

CSF cerebrospinal fluid, *mg* milligrams, *μL* microliters, *dL* deciliters, + plus, *C. dubliniensis*, *Candida dubliniensis*

Systems, Marcy-l'Etoile, France). It was sensitive to caspofungin, fluconazole, and voriconazole. The patient was started on IV liposomal amphotericin B (3 mg/kg per day) and flucytosine (2 g every 6 hours). Serial CSF testing showed improvement in leukocyte count and protein level during treatment (Table 1). Repeat MRI of the brain showed decreased hydrocephalus and leptomeningeal enhancement. The patient received 14 days of liposomal amphotericin B (3.5 g) and flucytosine. He was switched to IV fluconazole (400 mg daily) for 16 days and subsequently to oral fluconazole (200 mg daily). Unfortunately, the patient became increasingly obtunded, developed hypoxemic respiratory failure, renal failure, and decompensated liver disease and expired.

Discussion

We report the second case of meningitis due to *C. dubliniensis*. The first reported case was of a 48-year-old man who had undergone heart and lung transplantation and had received immunosuppressive medications and prophylaxis against opportunistic infections post-transplant [9]. He was diagnosed with *C. dubliniensis* fungemia which cleared with caspofungin treatment. He presented 2 months later with meningeal symptoms and was found to have *C. dubliniensis* in his CSF. He was subsequently treated with fluconazole and recovered. The authors hypothesized that the patient developed hematogenous seeding of the central nervous system (CNS), which became

clinically apparent in the setting of immunosuppression. As in our patient, the previous case had a CSF profile which showed marked pleocytosis and elevated protein, and similarly, the diagnosis was delayed. In contrast to our patient, this patient received previous antifungal therapy, which may have led to his survival.

Parameningeal involvement with *C. dubliniensis* has been described in 2 cases of spondylodiscitis. Both cases had increased susceptibility to infection in the setting of either HIV and HCV coinfection and cirrhosis or underlying HCV and IV drug use [11, 12]. Both cases presented with back pain, and diagnosis was made by direct needle biopsy or from culture fluid.

There have been over 50 previously reported cases of meningitis due to *C. albicans* [13–15]. Pleocytosis, low glucose, and elevated protein in the CSF are common findings [13]. *C. albicans* may be difficult to demonstrate on CSF smears. In one study, 2 cases of *C. albicans* were identified in CSF with real-time PCR assays, although the CSF smear for both cases was negative [16]. Multiple lumbar punctures may be necessary to identify the organism [7, 8].

In contrast to rare cases of *C. dubliniensis* meningitis, there are at least 25 reported cases of *C. dubliniensis* fungemia [9, 17–20]. Risk factors for *C. dubiniensis* fungemia include central catheters, recent broad-spectrum antibiotic use, immunocompromised state (including HIV, recent chemotherapy, leukemia, lymphoma), end-stage liver disease, and IV drug use. Our patient had risk factors for *C. dubliniensis* fungemia, specifically recent broad-spectrum antibiotic use, end-stage liver disease, and recent central line placement. Although he did not have documented fungemia, we speculate that he had low-level fungemia with hematogenous seeding to his CSF prior to hospitalization.

Candida dubliniensis may be misidentified as *C. albicans* given its phenotypic and genotypic similarities. More recently, it is identified by MALDI-TOF MS. In our laboratory, MALDI-TOF MS showed a 99.9 % match to *C. dubliniensis* using the Food and Drug Administration (FDA)-approved VITEK MS in vitro diagnostic (IVD) database, which is well differentiated from *C. albicans*. This was confirmed through 28S sequencing with 100 % identity to type strains [21].

The optimal treatment for *C. dubliniensis* infections is not clear. In vitro studies for *C. dubliniensis* demonstrate that only amphotericin B is fungicidal, while flucytosine is fungicidal at high minimum inhibitory concentrations. In contrast, azoles such as fluconazole, voriconazole, and posaconazole are largely fungistatic [22] and resistance has been described. It is possible that in the first reported case of *C. dubiniensis* meningitis, the initial azole treatment had inadequate penetration into the CSF as the patient developed meningitis 2 months after prior antifungal therapy [9]. In the first case of spondylodiscitis due to *C. dubliniensis* [12], the patient was successfully treated with 3 months of fluconazole. In the second case of spondylodiscitis, treatment consisted of 4 weeks of liposomal amphotericin B and 32 weeks of fluconazole with good outcome [11]. Unfortunately, our patient did not survive, possibly due to the fulminant nature of his meningitis, and the delay in diagnosis and treatment. Although CSF sterilization was achieved, it is unclear whether the azole penetration into the CSF was optimal. While *C. dubliniensis* has been considered to be less virulent compared to *C. albicans*, mortality associated with *C. dubliniensis* fungemia is higher compared to *C. albicans*. This may be due to higher levels of resistance to antifungal agents [23, 24] or the greater degree of immunosuppression in the affected hosts.

In summary, we describe the second case of meningitis due to *C. dubliniensis*. While rare, this case demonstrates the potential of this pathogen to cause severe disease. A high index of suspicion in the appropriate host is necessary to prevent delays in diagnosis. Optimal therapy remains to be defined.

Author Contributions AY collected and analyzed the data, reviewed all relevant literature, and wrote the first draft of the manuscript. VL, MV, DP, and AY edited and revised the manuscript. All authors have seen and approved the final version for submission. All authors contributed significantly to this work.

Compliance with Ethical Standards

Conflict of interest None.

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