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Fatal chronic meningitis caused by *Candida dubliniensis* after liver transplantation

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ABSTRACT

We report a case of fatal chronic *Candida dubliniensis* meningitis complicated by severe hydrocephalus secondary to liver transplantation, in which diagnosis was considerably delayed.

1. Introduction

Chronic meningitis caused by candida is rare and often difficult to diagnose. *Candida dubliniensis* meningitis has only been described in very few cases. We report a case of fatal chronic *C. dubliniensis* meningitis complicated by hydrocephalus secondary to liver transplantation, in which diagnosis was considerably delayed. To our knowledge, this is the seventh reported case of *C. dubliniensis* meningitis [1–6].

1.1. Case

Three months after liver transplantation, a 32-year-old male was admitted (day 0) because of four weeks of headache, nausea and intermittent fever. His previous medical history included ulcerative colitis, diabetes and progressive liver failure secondary to primary sclerosing cholangitis with autoimmune hepatitis. After liver transplantation, recovery was delayed because of biliary strictures and cholangitis from which he recovered without signs of rejection or invasive candidiasis. Before admission, standard dosages of tacrolimus, mycophenolate mofetil and prednisone were used for the prevention of rejection. No antifungal prophylaxis was given.

On admission, his headache was severe, but neurological examination was unremarkable. Lumbar puncture revealed a cerebrospinal fluid (CSF) white cell count of 438 × 10^6 with 55% neutrophils, protein 1.1 g/L and glucose 3.0 mmol/L (Table 1). Microscopy, extended CSF cultures and broad-range PCR were negative for bacteria, vira and fungi. CT and MRI of the brain as well as CSF opening pressure were normal. Empirical treatment with meropenem, ciprofloxacin and acyclovir were initiated without improvement. Subsequently, lumbar punctures were repeated, which demonstrated decreasing pleocytosis and increasing CSF protein, but remained negative by culture and PCR. Repeated MRI and CT was also unremarkable. CSF opening pressure was not at this time measured. Initially, the severity headache was fluctuating, but worsened at day +21 with development of hydrocephalus, requiring external ventricular drainage (EVD). At day +28, a fourth CSF culture finally grew *C. dubliniensis,* which at this time also was detected by 18s rRNA PCR of the CSF. Species identification was done at the National Reference Unit of Mycology, Statens Serum Institut, as previously reported [7]. Beta-D-glucan testing was not performed.

Treatment with ambisome and flucytosine was initiated and the EVD drain was changed with addition of intrathecal amphotericin B. Because of persistent side-effects, flucytosine was replaced with high dose fluconazole. Repeated attempts of EVD weaning failed because of persisting hydrocephalus, which lead to placement of a ventriculoperitoneal (VP) shunt. At this time, the patient's condition improved somewhat. Repeated CSF cultures were negative, but CSF inflammation persisted (Table 1). At day +70, MRI demonstrated subarachnoidal leptomeningeal enhancement and discrete signal changes in the medulla oblongata. Amphotericin B was discontinued after +84 days of treatment and fluconazole 800 mg x1 was continued. During the next weeks, his clinical condition deteriorated again with MRI showing severe enhancement and oedema at the cisterna magna with stenosis of the aqueduct. Treatment with Amphotericin B and flucytosine was restarted, the VP shunt was removed, and intrathecal caspofungin was added. Empiric antibiotics for suspected EVD associated ventriculitis was also given.

Despite aggressive antifungal therapy, his condition deteriorated

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Table 1
Cerebrospinal fluid findings.

Week of admission	Nucleated cells (x 10 ^{6}/l)	**Neutrophils (x 10 ^{6}/l)**	**Protein (g/dl)**	Microbiology
1	438	243	1.05	Negative
2	269	101	1.21	Negative
3	211	99	1.62	Negative
4	91	43	0.66	Culture/PCR 18s rRNA [d]
5	244	217	0.77	[a] Culture [d]
6	119	96	0,86	–
7	45	22	0.52	–
8	16	11	0.26	–
9	20	11	0.23	–
10	73	42	> 6	–
11	49	37	2	–
12	292	173	> 6	-[b]
13	–	–	–	–
14	–	–	–	–
15	66	24	> 6	–
16	20	13	0.19	[c]
17	67	35	0.45	–
18	32	12	0.58	

Candida dubliniensis, sensitive to Voriconazol (MIC: 0.008 mg/L), Amphotericin B (MIC: 0.032 mg/L), Fluconazol (MIC: 0.125 mg/L).The majority of CSF samples after week 4 were obtained from external ventricular drainage.

[a] After 3 days of treatment.

[b] PCR negative.

[c] A few yeasts by microscopy. CSF culture negative, Candida mannan antigen in CSF > 500 pg/ml. PCR not done.

[d] Positive. - Culture negative.

slowly with increasing double vision, memory loss and tremors. By MRI increased blockage of the foramen Monroe and oedema of the medulla oblongata was found. A few yeasts and an elevated Candida mannan antigen level were at this time detected in the CSF, but cultures remained negative. Further reduction of the immunosuppressive therapy was attempted, however, acute on chronic liver graft rejection developed and the patient died shortly after. Investigations (without DNA sequencing) for primary immunodeficiencies were negative.

2. Discussion

Candida is as rare cause of CNS infection among immunocompromised patients and associated with mortality rates over 50% [8,9]. Usually, candida meningitis is caused by *C.albicans*, however cases of *C. dubliniensis* have been reported after 2008, in which the first case was described [1]. *C. dubliniensis* is closely related to *C. albicans*, which it resembles by the ability to produce hyphae and chlamydospores. Infection models have suggested that *C. dubliniensis* is less pathogenic than *C. albicans* [10]. However, invasive candidiasis (IC) caused by non-albicans species are increasing [11,12]. A recent Danish nationwide study observed a doubling in the incidence of *C. dubliniensis* fungemia from 2012 to 2015 [12]. Previous reports of *C. dubliniensis* meningitis have been related to heart and lung transplantation [1,4], IVDU [5,6], CARD 9 immunodeficiency [3] and cirrhosis [2]. In two of these cases, relapse of *C. dubliniensis* meningitis was observed after 8 week and 6 months of initial therapy, respectively.

The diagnosis of candida as a cause of chronic meningitis is often challenging. In most cases, initial CSF findings are pleocytosis with granulocyte predominance and diagnosis may be delayed due to negative CSF culture. In the present case, several repeated CSF cultures and PCR were negative before the final verification of *C.dubliniensis*. Similar difficulties have been described previously. In a case of *C. albicans* meningitis secondary to liver transplantation reported by Ralph et al., biopsy from the brain and meninges and four repeated CSF cultures were culture and microscopy negative before CSF grew *C. albicans* [13]. More recently, Wilson et al. reported a 26-year-old IVDU with diffuse brainstem and spinal cord leptomeningitis in which *C. dubliniensis* was first established by metagenomic next-generation sequencing of CSF after 6 months of extensive negative diagnostic studies including repeated cultures, CSF 18s/6s rRNA PCR and meningeal biopsies [5].

Despite development of severe meningitis and hydrocephalus, initial repeated MRI did not show meningeal inflammation or raised ICP, similar to other case reports [13]. The present case of candida meningitis has several clinical features similar to cryptococcal meningitis in which initial MRI and CSF opening pressure may fail to demonstrate meningitis with raised CNS ICP, and in which hydrocephalus is associated with high mortality [14–17].

The optimal treatment of candida meningitis is not established, but usually requires intensive prolonged treatment with combination fungicidal treatment such as amphotericin B and flucytosine. In this case, a combination of complicated hydrocephalus, antifungal treatment toxicity and liver failure was fatal despite negative CSF cultures during high-dose systemic combination and intra-thecal antifungal therapy.

The reason for candida meningitis in the present case is unclear. Candida meningitis is caused by hematogenous spread with secondary cross of the blood brain barrier after which, Candida is able to form biofilms that evade the CNS microglial defense [18]. However, in several case reports, preceding candidemia/IC were not observed. Although liver transplantation is associated with higher risk of invasive fungal infections compared to other SOT, our patient was young, had no previous evidence of IC and did only receive routine immunosuppressive treatment [19,20] In theory, the patient may have had an innate immunodeficiency in keeping with his history of autoimmune hepatitis and colitis ulcerosa, however permission to DNA exome sequencing was not granted.

C. dubliniensis as a cause of chronic meningitis remains rare but appears to be increasing in parallel with the increase in non-albicans invasive candidiasis. Diagnosis and management remain challenging, particularly in case of complicated hydrocephalus, which in our patient was fatal. In culture negative chronic meningitis, candida should be considered and may require repeated CSF investigations. Recent publications have suggested that molecular methods such as metagenomic next-generation sequencing may facilitate early diagnosis [5], however the diagnostic performance of DNA based CSF methods are not established, as shown in our case, in which initial PCR analysis were negative and it remains important to obtain large CSF volumes for specific fungal culturing.

Declaration of competing interest

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