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

Mariam Gheshlaghi, Jannik Helweg-Larsen

Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Copenhagen, 2100, Denmark

**ARTICLE INFO**

**Keywords:**
- Candida dubliniensis meningitis
- Chronic meningitis
- Liver transplantation
- Invasive candidiasis

**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 \(438 \times 10^6\) 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 ambsion 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...
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.

* After 3 days of treatment.

PCR negative.

a A few yeasts by microscopy, CSF culture negative, Candida mannan antigen in CSF > 500 pg/mL. PCR not done.

b Positive. - Culture negative.

slowly with increasing double vision, memory loss and tremors. By MRI and PCR were negative before the granulocyte predominance and diagnosis may be delayed due to ne-

ter cases of C. dubliniensis [4,6], CARD 9 immunode-

Similar di-

Table 1

| Week of admission | Nucleated cells (x 10^3/l) | Neutrophils (x 10^3/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 |
| 5                 | 244                      | 217                   | 0.77         | Culture *   |
| 6                 | 119                      | 96                    | 0.86         | –           |
| 7                 | 45                       | 22                    | 0.52         | –           |
| 8                 | 11                       | 11                    | 0.26         | –           |
| 9                 | 20                       | 11                    | 0.23         | –           |
| 10                | 73                       | 42                    | > 6          | –           |
| 11                | 49                       | 37                    | 2            | –           |
| 12                | 292                      | 173                   | > 6          | –           |
| 13                | –                        | –                     | –            | –           |
| 14                | –                        | –                     | –            | –           |
| 15                | 66                       | 24                    | > 6          | –           |
| 16                | 20                       | 13                    | 0.19         | –           |
| 17                | 67                       | 35                    | 0.45         | –           |
| 18                | 32                       | 12                    | 0.58         | –           |

Candida 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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] S.J. van Hal, D. Stark, J. Harkness, D. Marriott, Candida dubliniensis meningitis as delayed sequel of treated C. dubliniensis fungemia, Emerg. Infect. Dis. 14 (2008) 327–329.
[2] A. Yamahiro, K.H.V. Lau, D.R. Peaper, M. Villanueva, Meningitis caused by Candida dubliniensis in a patient with cirrhosis: a case report and review of the literature, Mycopathologia 181 (2016) 589–593.
[3] A. Deswiniak, R.P. Gazendam, A.T.J. Tool, M. van Houdt, M.H. Jansen, J.L. van Hamme, E.M.M. van Leeuwen, D. Roos, E. Scalais, C. de Beaufort, H. Janssen, T.K. van den Bergh, T.W. Kuijpers, Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency, Blood 121 (2013) 2385–2392.
[4] S. Herrera, P. Pavone, D. Kumar, L. Singer, A. Kumar, C. Chaparro, S. Keshavye, S. Husain, C. Rotstein, Chronic Candida dubliniensis meningitis in a lung transplant recipient, Med. Mycol. Case Rep. 24 (2019) 41–43.
[5] M.R. Wilson, B.D. O’Donovan, J.M. Geall, H.A. Sample, F.C. Chow, J.P. Betjeman, M.P. Shah, M.B. Richle, M.P. Gorman, R.A. Haji-Ali, L.H. Calabrese, K.C. Zorn, E.D. Chow, E.D. Greenlee, J.H. Blum, G. Green, L.M. Khan, D. Banerji, C. Langelier, C. Bryson-Cahn, W. Harrington, J.R. Lingappa, N.M. Shanbash, A.J. Green, B.J. Brew, A. Soldatos, L. Strnad, S.B. Doernberg, C.A. Jay, V. Douglas, S.A. Josephson, J.L. DeRisi, Chronic meningitis investigated via metagenomic next-
generation sequencing. JAMA Neurol. 75 (2018) 947–955.
[6] N.H. Andrew, R.P. Ruberu, G. Gabb, The first documented case of Candida dublieniensis leptomeningeal disease in an immunocompetent host, BMJ Case Rep. (2011) 4–7.
[7] M.C. Arendrup, E. Dzajic, R.H. Jensen, H.K. Johansen, P. Kjaeldgaard, J.D. Knudsen, L. Kristensen, C. Leitz, L.E. Lemming, L. Nielsen, B. Olesen, F.S. Rosenvinge, B.L. Røder, H.C. Schønheder, Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: data from a nationwide fungaemia surveillance programme, Clin. Microbiol. Infect. 19 (2013).
[8] R.A. Voice, S.F. Bradley, J.A. Sangeorzan, C.A. Kauffman, Chronic candidal meningitis: an uncommon manifestation of candidiasis, Clin. Infect. Dis. 19 (1994) 60–66.
[9] K. Góral ska, J. Blasz kowska, M. Dzikowiec, Neuroinfections caused by fungi, Infection 46 (2018) 443–459.
[10] G.P. Moran, D.C. Coleman, D.J. Sullivan, Candida albicans versus Candida dublinerensis: why is C. albicans more pathogenic? Internet J. Microbiol. 2012 (2012).
[11] Z. Khan, S. Ahmad, L. Joseph, R. Chandy, Candida dublieniensis: an appraisal of its clinical significance as a bloodstream pathogen, PLoS One 7 (2012) e32952.
[12] K.M.T. Astvad, H.K. Johansen, B.L. Røder, F.S. Rosenvinge, J.D. Knudsen, L. Lemming, H.C. Schønheder, R.K. Hare, L. Kristensen, L. Nielsen, J.B. Gerten, E. Dzajic, M. Pedersen, C. Østergaard, B. Olesen, T.S. Sandergaard, M.C. Arendrup, Update from a 12-year nationwide fungaemia surveillance: increasing intrinsic and acquired resistance causes concern, J. Clin. Microbiol. 56 (2018) 1–15.
[13] A.D. Ralph, Z. Hussain, Chronic meningitis caused by Candida albicans in a liver transplant recipient: usefulness of the polymerase chain reaction for diagnosis and for monitoring treatment, Clin. Infect. Dis. 23 (1996) 191–192.
[14] R.A. Sarkis, M. Mays, C. Isada, M. Ahmed, MRI findings in cryptococcal meningitis of the non-HIV population, The Neurologist 19 (2015) 40–45.
[15] P.R. Williamson, J.N. Jarvis, A.A. Panackal, M.C. Fisher, S.F. Molloy, A. Loyse, T.S. Harrison, Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy, Nat. Rev. Neuro. 13 (2017) 13–24.
[16] A. Loyse, A. Moodley, P. Rich, S.F. Molloy, T. Bicanic, L. Bishop, W.I.D. Rae, A.I. Bhigjee, N.D. Loubser, A.J. Michowicz, D. Wilson, T.S. Harrison, Neurological, visual, and MRI brain scan findings in 87 South African patients with HIV-associated cryptococcal meningoencephalitis, J. Infect. 70 (2015) 668–675.
[17] J. Cherian, R.L. Atmar, S.P. Gopinath, Shunting in cryptococcal meningitis, J. Neurosurg. 125 (2016) 177–186.
[18] G.W. Koutsouras, R.I. Ramos, L.R. Martinez, Role of microglia in fungal infections of the central nervous system, Virulence 8 (2017) 705–718.
[19] M. Nagao, Y. Fujimoto, M. Yamamoto, Y. Matsumura, T. Kaido, S. Takakura, S. Uemoto, S. Ichiyama, Epidemiology of invasive fungal infections after liver transplantation and the risk factors of late-onset invasive aspergillosis, J. Infect. Chemother. 22 (2016) 84–89.
[20] P.G. Pappas, R.D. Alexander, D.R. Andes, S. Hadley, C. a Kauffman, A. Freifeld, E.J. Anaissie, L.M. Brumble, L. Herwaldt, J. Ito, D.P. Kontoyiannis, G.M. Lyon, K. a Marr, V. a Morrison, B.J. Park, T.F. Patterson, T.M. Perl, R. a Oster, M.G. Schuster, R. Walker, T.J. Walsh, K. a Wannemuehler, T.M. Chiller, Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET), Clin. Infect. Dis. 50 (2010) 1101–1111.