Chronic *Candida dubliniensis* meningitis in a lung transplant recipient

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ABSTRACT

Candida spp. are common colonizers of the oral mucosa and respiratory tract in lung transplant recipients. Although thought to be non-pathogenic in most cases, donor derived infections related to Candida spp. have been described. Among the manifestations of invasive candidiasis, chronic meningitis is one of the rarest and one of the most challenging to diagnose, due to the indolence of the disease and the low yield of the CSF cultures. It is associated with severe morbidity and a high mortality. Fungal PCR and BD glucan assays can be assistance in its diagnosis, although these tests are not widely available. We report a case of a possible donor derived *Candida dubliniensis* infection in a lung transplant recipient, who initially presented with empyema that was treated successfully, but subsequently developed chronic meningitis. Diagnosis was delayed due to the low yield of CSF cultures, and was confirmed with fungal PCR and BD glucan assay.

1. Introduction

Although candidemia and other forms of invasive candidiasis are common nosocomial infections [1], *Candida* spp. meningitis is a rare condition most often found in new-borns [2] and patients that have undergone neurosurgical procedures or have placement of a shunt [3]. In the latter situation, it is believed to arise as a result of metastatic seeding following a *Candida* bloodstream infection. Signs and symptoms can be similar to those of bacterial meningitis such a fever, neck stiffness, headache or altered mental status; however, in chronic *Candida* meningitis, the signs and symptoms tend to be more insidious emulating conditions such as tuberculous or cryptococcal meningitis, and therefore the diagnosis is often delayed for months.

Among *Candida* species, *Candida albicans* [4] accounts for most of the cases of *Candida* meningitis, followed by *Candida parapsilosis* and *Candida tropicalis*. There are only three reported cases with *Candida dubliniensis* meningitis [5–7]. Previously reported patients were: a heart-lung transplant recipient, a cirrhotic patient and a drug user, respectively. The heart-lung recipient developed meningitis 3 months after being successfully cured of candidemia and empyema.

Herein, we present a case of chronic *Candida dublinensis* meningitis in a lung transplant recipient possibly resulting from a donor derived infection.

2. Case

A 74-year-old man with a past history of hypertension, type II diabetes mellitus and hypothyroidism underwent single right lung transplant (day +0) for idiopathic pulmonary fibrosis. The transplant surgical procedure was uneventful. There was a CMV serological mismatch (donor positive and recipient negative). The patient did not receive induction therapy and his maintenance immunosuppressive regimen consisted of prednisone, mycophenolate mofetil and cyclosporine. The donor was made available through expanded donor criteria and was hepatitis C virus nuclear antigen positive. The donor bronchoalveolar lavage (BAL) cultures demonstrated a heavy growth of *Candida albicans* and *C. dubliniensis*. The recipient post-transplant recipient BAL was negative for fungi. After transplantation the recipient was placed on sofosbuvir - velpatasvir (Epclusa) therapy.

On day +25 after transplantation, the patient was readmitted to the hospital with hypoxia. A CT scan of the chest revealed a new pleural effusion. A pigtail catheter was placed to drain the pleural fluid, and the pleural fluid cultures grew *C. albicans* and *C. dubliniensis*. The blood cultures were negative. The patient received antifungal therapy with caspofungin for 6 weeks (from day +29 to day +71) for invasive candidiasis with resolution of the effusion. Azoles were avoided at this point to avoid interaction with calcineurin inhibitors early post-transplant.

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Table 1
CSF characteristics and cultures.

Date	WBC X10^6/L	Neutrophil (%)	RBC X10^6/L	Proteins g/L	Glucose mmol/L	Culture
2017/11/24	700	13	22000	NA	NA	Negative
2018/2/21	473	80	16	0.63	2.0	Negative
2018/3/2	30	35	84	0.57	3.1	1 colony *C. dubliniensis*
2018/4/6	34	0	0	0.72	4.1	Negative
2018/6/5	438	80	8	1.18	3.5	Negative
2018/6/15	51	46	5300	1.27	4.2	Negative
						BD glucan 500 pg/mL
						PCR positive for *C. dubliniensis*

NA: not available. WBC: white blood cells, RBC: red blood cells. Glucose mmol/L, Proteins g/L (normal range 0.15–0.45), BD glucan pg/mL (normal range 60–79).

Approximately, on day +30 day after the transplant, the patient started developing a headache. A CT scan of the head was normal, and a lumbar puncture showed negative microbiological findings (Table 1). The headache was attributed to aseptic meningitis secondary to his cyclosporine or his sofosbuvir - velpatasvir. He was discharged from the hospital shortly thereafter but, the headache persisted, accompanied by lethargy. He was admitted again to the hospital on day +111 for further workup. CT of the head and MRI were normal. MRI of the spine showed degenerative changes. A repeat lumbar puncture was performed and revealed an increased white blood cell count, with low glucose and high proteins (Table 1). Both antibacterial and antifungal therapy were initiated (ampicilin, ceftriaxone and voriconazole). The following were performed: Cryptococcus serum and CSF antigen, Histoplasma and Blastomyces serology, serum galactomannan, AFB stain and cultures, Lyme disease serology, viral PCR for CMV, VZV, EBV, HSV 1, HSV 2, HHV6, and West Nile virus. All of the aforementioned serological tests were negative. A lumbar puncture was repeated nine days after the first one to assess response. Table 1 shows repeated CSF findings. The second lumbar puncture cerebral spinal fluid (CSF) cultures grew 1 colony of C. *dubliniensis,* identified by means of MALDI-TOF and culture. Table 2 shows the antifungal susceptibilities. After eighteen days of voriconazole he was switched to oral fluconazole 400mg po once a day and discharged home to complete a total of eight weeks of treatment. Voriconazole therapeutic drug monitoring was performed during the time of treatment.

Four weeks after finishing the treatment he was readmitted to the hospital on day +208 with fever and sternal pain. CT scan of the chest revealed osteomyelitis of the sternum. He was placed on broad spectrum antibiotics and taken to the OR for debridement. Four samples grew *Candida tropicalis*. His systemic antibiotics were stopped, and he was started on caspofungin intravenously (from day +215 to day +224). Concomitantly he started complaining again of headache and gradually become more lethargic. A new CT scan and MRI of the brain were performed and did not reveal any abnormalities. A lumbar puncture was repeated (see Table 1). CSF revealed an increased white blood cell count, and the previous history of Candida meningitis the patient was switched to intravenous liposomal amphotericin B (L-AmB). CSF cultures and viral PCRs were again negative. The patient started to improve after one week of L-AmB. A lumbar puncture was repeated ten days later showing improvement in the white blood cell count but still

had a high protein content. Further testing of the CSF was performed including a B-D glucan assay (Glucatell, Associates of Cape Cod, East Falmouth, MA) and fungal PCR that were completed in external laboratories (Pan-fungus Polymerase Chain Reaction followed by DNA sequence analysis (ITS-2 (Internal transcribed spacer region) rRNA gene); performed at the Hospital for Sick Children, Toronto, Ontario). The BD glucan was > *500* pg/mL and the fungal PCR was positive for *C. dubliniensis*. After two weeks of L-AmB the patient was switched to oral voriconazole and continued to improve.

An inquiry was made about the other lung recipient, who happened to have *C. dubliniensis and C.albicans* fungemia 13 days after transplant, as well as *C. tropicalis* and *C. albicans* in his post-transplant BAL that was treated successfully with Caspofungin intravenously for five weeks (Table 2 shows antifungal susceptibilities). Unfortunately, we were unable to access susceptibility from the donor BAL isolates, as the organs were retrieved from another country.

3. Discussion

This case illustrates a possible donor-derived infection, even if we couldn't perform genetic studies to confirm it. The rarity of the species of *Candida: C dublieniensis,* found in donor and both recipients (with similar fungograms) makes it highly likely. This case also raises the issue of whether treatment of Candida in donor BAL secretions in lung transplant recipients in centers where universal antifungal prophylaxis is not practiced. In lung transplant recipients, *Candida* is a common colonizer of the respiratory tract and often not considered pathogenic, although it has been reported as donor-derived infection [8]. Most centers employ universal antifungal prophylaxis for 3 months post-transplant. In those that use pre-emptive prophylaxis it would be prudent to give antifungal prophylaxis whenever donor cultures yield *Candida* until the integrity of the anastomoses has been confirmed or if the recipient has received lymphocyte depleting agents [9].

Other questions that arise from this case are if this patient might have had enhanced host susceptibility due to a possible genetic dectin [10] abnormality that made him more susceptible to invasive *Candida* infections (as he had empyema, osteomyelitis (with a different *Candida* strain)) and meningitis and if he had a fungemia that was undiagnosed after transplant could have led to seeding of the CNS. Patients with invasive candidiasis should be followed closely as the may develop further metastatic infection after an apparent cure.

Diagnosis of chronic *Candida* meningitis can be challenging due to the poor yield of CSF cultures [11]. In chronic meningitis, as the *Candida* burden is low, the diagnosis may be considered with obvious symptoms and signs of meningitis and the isolation of *Candida* from other sites. The low CSF yield of Candida was exemplified in our case as only one of the 5 lumbar punctures showed growth of *Candida*. CSF characteristics usually show moderately increased white blood cell count that can be neutrophilic or lymphocytic, with low glucose and high protein content [11]. Other tests such as the BD-glucan assay [12], fungal PCR or metagenomics [7] can be helpful in assisting diagnosis and monitoring response. Unfortunately, we were unable to monitor BD

Table 2
Candida dubliniensis antifungal susceptibilities.

Antifungal	CSF MIC mg/L	Other lung recipient Blood culture MIC mg/L
Amphotericin B	0.5	0.25
Anidulafungin	0.12	0.12
Caspofungin	0.06	0.06
Fluconazole	0.25	0.25
Itraconazole	0.06	0.06
Micafungin	0.03	0.03
Posaconazole	0.03	0.03
Voriconazole	Less than 0.008	Less than 0.008

glucan levels as there were no subsequent CSF samples. Imaging is useful if there is presence of microabscesses.

Initial treatment with L-AmB and Flucytosine due to the CSF penetration until there is clinical improvement. It is then recommended to continue therapy with an azole possessing good CNS penetration such a fluconazole or voriconazole guided by antifungal susceptibilities [13]. Echinocandins should be avoided due to their poor CSF penetration [14]. Duration of therapy is unclear and is generally guided by clinical and CSF response or resolution of microabscesses if present.

Data for mortality rates are mainly available for neonates. There are no clinical trials for Candida chronic meningitis. Only case series of patients with chronic *Candida* meningitis have reported a mortality rate of 53% [11].

One of the most important lessons from this case is that CSF culture for diagnosis of chronic *Candida* meningitis has a poor yield, if suspected a BD glucan assay can be helpful, although this is not standardized, and it is not specific. Fungal PCR can be very useful avoiding a delay in the diagnosis. Duration of therapy in immunocompromised patients and reduction in immunosuppressive therapy are other questions that have yet to be clarified.

Conflict of interest

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