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Meningitis caused by *Candida dubliniensis* in a patient with liver cirrhosis: A case report and review of the literature

Muhammad Absar [a,*,1], Ahmed Alduwayrij [b,1], Abdulmajeed Al-Arfaj [c], Zafar Shah [d], Fahad Nashmy [a], Mohamed Tahar Yacoubi [a]

[a] Department of Pathology and Laboratory Medicine, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, AlAhsa, Saudi Arabia
[b] Department of Medical Education, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, AlAhsa, Saudi Arabia
[c] Infection Prevention & Control Program, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, AlAhsa, Saudi Arabia
[d] Intensive Care Unit, King Abdulaziz Hospital, Ministry of the National Guard-Health Affairs, AlAhsa, Saudi Arabia

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ABSTRACT

Candida meningitis is almost always caused by *Candia albicans*, but other species, such as *Candida dubliniensis*, can cause it on rare occasions. *C. dubliniensis* is increasingly linked to immunocompromised hosts but also affects immunocompetent hosts. To the best of our knowledge, we present the ninth (9th) case of *C. dubliniensis* meningitis, the first from Saudi Arabia. A 70-year-old woman with multiple comorbidities presented with confusion, poor oral intake, and left upper limb swelling for two weeks. *C. dubliniensis* was isolated and treated with liposomal amphotericin and anidulafungin. The scarcity of such infections makes the best treatment regimen undetermined.

1. Introduction

Candida dubliniensis was first identified in the oropharynx of HIV-positive patients in Ireland. Candida meningitis is rare and mostly attributed to *C. albicans* [1]. Risk factors for invasive candidiasis include neurosurgical interventions, previous treatment with antibiotics, parenteral nutrition, abdominal surgery, and an immunocompromised state such as HIV/AIDS, malignancy, or chronic steroid use [2]. To the best of our knowledge, the literature only reports eight (08) cases of *C. dubliniensis* meningitis (Table 1). We report the ninth (9th) case, the first from Saudi Arabia, which was further aggravated by urosepsis and septic shock due to New Delhi metallo-β-lactamase producing *K. pneumoniae* near the end, eventually leading to the patient's death.

2. Case presentation

The patient was a 70-year-old woman with diabetes, hypertension, dyslipidaemia, osteoarthritis, bronchial asthma, heart failure with preserved ejection fraction, liver cirrhosis secondary to NAFLD, grade II oesophageal varices that needed ligation, and end-stage renal disease (ESRD) on permcath-access haemodialysis with adherence challenges. The patient presented with symptoms of confusion, poor oral intake, fatigue, visual hallucinations, and left upper limb swelling. On physical examination patient was found confused with a Glasgow Coma Scale (GCS) of 10/15. She was hypothermic, her blood pressure was 107/65 mmHg, and her oxygen saturation was 98 % on room air. The left-forearm was swollen with no redness or discharged present around the left permcath access site. Basilar crackles were noted upon auscultation with normal heart sounds and no murmurs. Fundoscopic examination revealed no signs suggestive of fungal chorioretinitis. The rest of physical examination were unremarkable. For chronic osteoarthritis, the patient was taking tramadol (50mg OD), meloxicam (7.5mg OD), and diclofenac sodium gel (1 % gel). Her lab results upon admission were: Ammonia 80 μmol/L (normal range: 18–72 μmol/L), estimated glomerular filtration rate (eGFR) 18 ml/min/1.73m2 (normal range: ≥60 ml/min/1.73m2), Lactic acid 2.72 mmol/L (normal range: 0.5–2.2 mmol/L), C-reactive protein (CRP) 131.1 mg/L (normal range: ≤1.2 mg/L), bilirubin direct 17.1 μmol/L (normal range: ≤8 μmol/L), bilirubin total 41.3 μmol/L (normal range: 3.4–20.5 μmol/L), albumin 19 g/L (normal range: 32–46 g/L), Troponin-I 106.3 pg./ml (normal range

* Corresponding author.
E-mail address: MASHWANI82@gmail.com (M. Absar).
[1] Equal contribution.

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female: ≤15 pg./ml). Unremarkable brain CT and upper limb extremities. Doppler ultrasound showed subcutaneous edema without DVT. On day0, she was started on vancomycin (1000 mg intravenously) and piperacillin-tazobactam (2.25 gm intravenously every 12 hours), with an additional 0.75 gm dose after each haemodialysis session. Day+2, the peripheral blood culture was flagged positive and gram stain result showed budding yeast (Fig. 1a), and fluconazole (100 mg intravenously once a day) was initiated. The urine culture also grew yeast (day+3). *C. dubliniensis* was identified by using matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF), and the antifungal susceptibility was determined by using the Vitek-II, YST08 card (BioMérieux) and E-test (Liofilchem). Antifungals minimum inhibitory concentration (MIC) in microgram/millilitre (μg/ml) were as following: amphotericin B (MIC: ≤0.25), flucytosine (MIC: ≤1), voriconazole (MIC: ≤0.12), fluconazole (MIC: 4), anidulafungin (MIC: 0.016), and micafungin (MIC: 0.125). The infectious disease (ID) team changed antifungal treatment to anidulafungin 200 mg intravenously as a loading dose, followed by a maintenance dose of 100 mg intravenously every 24 hours (day+4) (refer to Fig. 1a, b, and c). On day+5, haemodialysis catheter removal and culture were requested due to a severe suspicion of catheter-related candidemia. Before removing the catheter line, the vascular team advised lowering the patient's INR. The patient developed hypotension, tachycardia, and hypothermia as a result of elevated lactic acid and ammonia levels; her GCS improved slightly to 14/15. *C. dubliniensis* was identified in two sets of repeat blood culture. The patient was transferred to the intensive care unit (ICU), given fluid and albumin resuscitation, a complete septic workup, and meropenem (500 mg intravenous every 24 hours) and vancomycin (1000 mg intravenous (day+7). On day+8, an echocardiogram revealed no new valvular lesions or vegetation. Her ophthalmology team examined her and discovered no evidence of fundus endophthalmitis. An abdomen ultrasound showed minor ascites, requiring a low (0.01 μg/kg/min) norepinephrine (NE) dose. The patient developed coagulopathy with a 1.6 INR, 16.8 PT, and 37.4 PTT; she received vitamin K for three days (day+9). On day+10, the culture tip grew *C. dubliniensis*, and the patient was hemodynamically stable, and was transferred to step-down. The patient had lactic acid build-up at 4.36, ammonia at 67, and there was a sudden drop in GCS from 14/15 to 9/15. An urgent brain CT was unremarkable. The patient was returned to the ICU for an urgent haemodialysis through left temporal femoral line. Day+11, two blood culture sets were sent for follow up. The patient's GCS was still low, and her brain MRI showed restricted diffusion (black arrows) in both lateral ventricles, suggesting early pus formation (Fig. 2a and b). CSF sample was obtained and sent for AFB and fungal cultures. CSF India ink preparation was negative for cryptococcus but showed two yeast-like morphologies as depicted in Fig. 1d. CSF cytology revealed many neutrophil aggregates and macrophages (Fig. 1e and f). The antifungal therapy was changed to liposomal amphotericin 400 mg IV every 24 hours. Neurosurgery team examined the patient without any further intervention and supported the ID team's antimicrobial recommendation. Patient's coagulopathy was improved after vitamin K therapy. The patient received fresh frozen plasma (FFP) and a repeat CSF culture was performed. Day+12, nasogastric tube (NG tube) was inserted and sample sent for TB PCR. The repeated blood cultures were once again positive for *C. dubliniensis* and dexamethasone was started (day+13). Patient completed the course of meropenem and vancomycin (day+15), fresh blood cultures showed *C. dubliniensis* and repeated CSF culture and fungal cultures also grew *C. dubliniensis*. Day+16, the patient condition was improved slightly and was shifted to step-down with ICU follow-up. AFB culture, TB PCR, and repeated CSF cultures were negative (day+17). On day+18, patient had low GCS (9/15), with high ammonia level of 120, received lactulose enema and passed bowl motion. Day+19, patient developed melena, with borderline blood pressure, ammonia level was 115 while lactic acid level was 3.42. Gastroenterology (GI) team was consulted, the patient's Blatchford score was 12 and it was concluded that the cause of bleeding was portal hypertension gastropathy rather than variceal bleeding. The patient received 10 mg vitamin K, four units of fresh frozen plasma, and octreotide for three days. One unit of packed red blood cells was given. Patient haemoglobin improved from 7.5 to 8.1, indicating slight improvement. Ammonia returned to normal, while lactic acid dropped from 3.42 to 2.33. One day later (day+20), melena stopped and patient showed some improvement (day+22). Patient ammonia level started to increase from 86 to 154. Patient received enema and passed bowl motion. GI team re-evaluated the patient and decided to postpone the upper endoscopy and stick to the previous plan. The first repeated blood culture was negative on day+23. (Day+24), the second blood culture turned out negative. On day+25, carbapenem resistant *Klebsiella pneumoniae* (NDM gene detected by PCR assay) was detected in the urine culture. The empirical antimicrobial regimen started with 160 mg intravenous gentamicin every 48 hours. On day+25, patient developed

Table 1
An overview of clinical features of *C. dubliniensis* meningitis [2,3,4,5,6–9].

Parameters	van Hal *et al.* 2008	Andrew et al., 2011	Yamahiro et al. 2016	Wilson et al., 2018	Herrera et al., 2019	Tahir et al., 2020	Gheshlaghi et al., 2019	Price et al., 2023	Current case
Location	Australia	Australia	USA	USA	Canada	USA	Denmark	Australia	Saudi Arabia
Gender/Age (Years)	M/48	M/25	M/60	F/26	M/74	F/27	M/32	M/30	F/70
Injecting drug user	NA	Yes	Yes	Yes	No	Yes	No	Yes	No
Hep C infection	NA	NA	Yes	Yes	No	Yes	No	Yes	No
Liver Cirrhosis	No	No	Yes	No	No	No	Yes	No	Yes
Immune-deficient?	Yes	No	Yes	NA	Yes	No	Yes	No	No
Symptoms prior to diagnosis	3 weeks	12 months	1 week	20 months	4 weeks	10 months	4 weeks	32 months	2 weeks
Systemic features of infection	weight loss	Absent	No	NA	NA	weight loss	severe headache	No	No
Abnormal MRI results	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Neurological deficit	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
Diagnostic methods	culture, blood, CSF and urine	culture CSF, fungal and dural tissue	culture CSF	NGS on CSF sample	culture CSF	culture CSF	culture CSF, CSF PCR	culture CSF	culture blood, urine, fungus, PCR CSF
Treatment	CAS + FCZ	L-AmB + FCZ	L-AmB + FCZ	unknown	CAS + L-AmB + VOR	AmB + FCZ	CAS + FCZ + L-AmB	L-AmB + FCZ	INN + L-AmB
Outcome	Survived	Survived	Expired	Survived	survived	Survived	Expired	Survived	Expired
Total treatment duration or follow-up	4.5 weeks	3 years	4 weeks	4 weeks	32 weeks	6 weeks	12 weeks	6 weeks	4 weeks

'Table 1 **legend:** NA: Not available, CAS: caspofungin + FCZ: fluconazole, L-AmB: liposomal amphotericin B, VOR: voriconazole, INN: anidulafungin, CSF: cerebrospinal fluid, NGS: next generation sequencing, PCR: polymerase chain reaction.

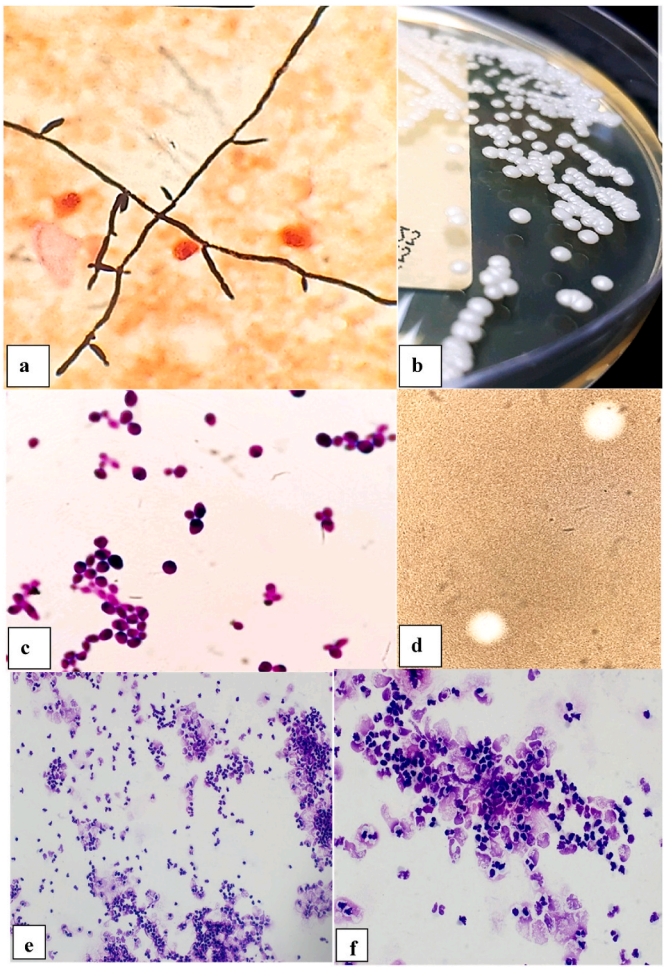

Fig. 1. (a) Gram stain from a positive blood culture, (b) growth of *C. dubliniensis* on Sabrouds dextrose agar after 48 hours, (c) gram stain of *C. dubliniensis* from colony, (d) suspected two yeasts as seen in India ink preparation. (e + f) CSF cytology; numerous aggregates of neutrophils identified along with macrophages (diff quick staining x200 and x400, respectively).

hypotension, needed oxygen support and also developed rapid atrial fibrillation. The critical care response team examined the patient and repeated septic workup. Patient was started Amiodarone, given vasopressor and transferred the ICU and intubated. On day+26, the patient became unresponsive to vasopressor support, was cardiac arrested, and died. Next day (day+27), *K. pneumoniae* (NDM gene detected) was also isolated from two blood culture sets.

3. Discussion

The majority of invasive candida infections (>90 %) are caused by *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei* [10]. In immunocompromised patients, Candidal CNS infections are rare and fatal, with over 50 % mortality [3]. *C. dubliniensis* caused the first candida meningitis case in 2008 [4]. *C. dubliniensis* is a pathogenic yeast species with phenotypic similarities to *C. albicans* [11]. Researchers have isolated *C. dubliniensis* from a variety of body sites, primarily the oral cavities of HIV and AIDS patients. Oral *C. dubliniensis* colonization in immunocompetent individuals can cause candidemia and invasive infections [1]. Our patient had chronic asthma and osteoarthritis, and was taking medications that suppressed the immune system and exposed him to infections. TNF-inhibitors and corticosteroids use is associated with fungal infections [12]. Case reports rarely report adult CNS Candida infections, but 6 of 8 (75 %) were adult patients (Table 1). Malignant blood disorders, solid tumours, organ transplants, intravenous drug use, diabetes, and HIV predispose patients to CNS candidiasis. Other intracranial devices and neurological procedures increase infection risk [5–7,13]. Table 1 summarises the eight meningitis cases reported in the literature from various continents [2,3,4,5,6–9]. Males caused 75 % of infections. The median age of all cases was 31 years and the average was 40.3 years (range: 25–74 years). Males outnumbered females 3:1. Injectable drug use, hepatitis C, immunodeficiency, liver cirrhosis, abnormal MRI findings, and neurological impairments were reported in 71.4 %, 66.7 % each, 57.1 %, 25 %, 87.5 %, and 62.5 % of cases (Table 1). The optimal treatment for *C. dubliniensis* meningitis is unknown due to the small number of reported cases. Treatment for the previous five cases included dual antifungal agents in 75 % of cases and triple antifungals in 25 %. The previous cases had a 25 % fatality rate (n = 2/8), possibly due to immunodeficiency or diagnosis and treatment delays. After *C. dubliniensis* candidemia was confirmed, the patient was treated with anidulafungin (an echinocandins with poor CNS penetration). However, the infection progressed to the meninges, and the

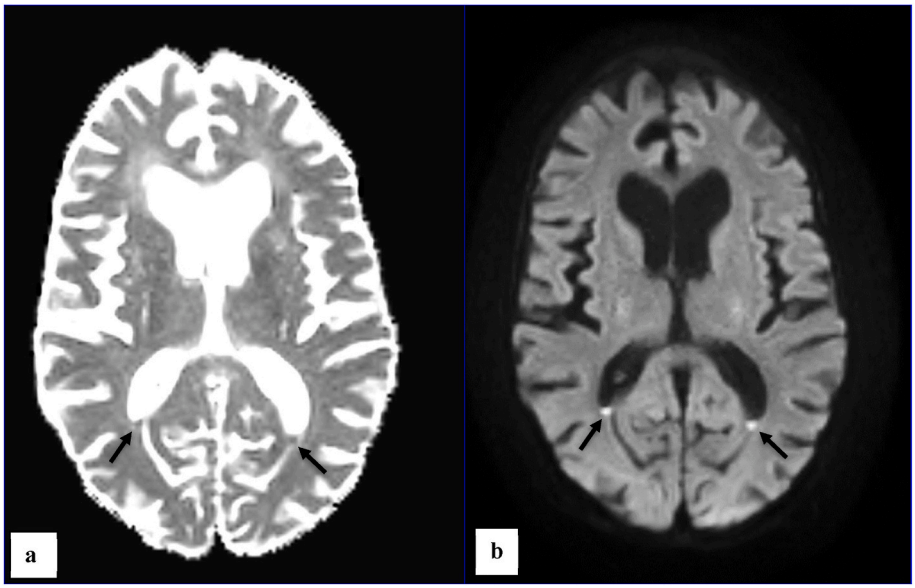

Fig. 2. (a+b): MRI without contrast showing signs of restricted diffusion (black arrows) in both ventricles.

treatment regimen was changed to liposomal Amphotericin-B (L-AmB). Our patient responded well to the antifungal treatment; however, because of multiple co-morbidities, including advanced age, diabetes, chronic kidney disease, liver cirrhosis-related secondary immunodeficiency, and secondary infection from carbapenem-resistant K. pneumoniae (NDM gene positive), our patient passed away from the illness.

Canada and Denmark reported one case, while the US and Australia reported three. Due to its increased tolerability and lower toxicity, liposomal Amphotericin-B (L-AmB) and other newer antifungals like azoles (fluconazole-FCZ and voriconazole-VOR) and echinocandins (caspofungin-CAS and anidulafungin-INN) are used more often in invasive fungal infections. L-AmB/FCZ combination therapy was used in 57.1 % of cases (Table 1). Recent incidence of *C. dubliniensis* has increased despite its low pathogenesis potential. Studies show that *C. dubliniensis* cases were rare before 1990. However, its prevalence increased over time, particularly among people living with HIV [14]. It is possible that antifungals pressure in treating oral thrush in AIDS patients has caused several *C. dubliniensis* isolates to be resistant to azoles, including fluconazole. In vitro exposure of susceptible isolates to fluconazole resulted in resistance, according to one study [11]. Fluconazole can also make *C. dubliniensis* more pathogenic by increasing epithelial cell adhesion and proteinase secretion [15]. *C. dubliniensis* has decreased in HIV patients due to modern treatments (HAART), which have delayed AIDS and reduced oral thrush rates [16]. Low numbers of candida meningitis make diagnosis difficult, and standard timber CSF culture yields low yields, especially in small volumes. All suspected cases require large amount of CSF culture.

The antifungal therapy was apparently effective as the repeated two blood cultures were negative for *C. dubliniensis* (day+23 and day+24). Day+24, culture urine grew carbapenem resistant *K. pneumoniae* (NDM gene positive). Day+25, the patient most likely developed urosepsis and septic shock, as evident by the need of oxygen support, hypotension and atrial fibrillation. The septic workup was repeated and patient condition further worsened on day+26, became unresponsive to vasopressor support and succumbed to the disease. Day+27, the sepsis cause was ultimately confirmed by positivity of two repeat blood cultures growing the same *K. pneumoniae* (NDM gene positive).

4. Conclusion

In conclusion, *C. dubliniensis* meningitis cases have high rates of morbidity and mortality. Due to their rarity, the best treatment is unknown. This is the first case report of *C. dubliniensis* infection from Saudi Arabia. Our study adds to the limited literature and emphasises the maintenance of an index of suspicion of *C. dubliniensis* infection as a rare differential diagnosis of meningitis in severely ill patients with multiple co-morbidities, including primary and secondary immunodeficiencies.

CRediT authorship contribution statement

Muhammad Absar: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ahmed Alduwayrij:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Abdulmajeed Al-Arfaj:** Writing – review & editing, Writing – original draft, Formal analysis. **Zafar Shah:** Writing – review & editing, Data curation. **Fahad Nashmy:** Data curation. **Mohamed Tahar Yacoubi:** Writing – review & editing, Data curation.

Patient consent

A written, signed consent was obtained from the patient guardian to publish this case report.

Declaration of competing interest

The authors declare no conflict of interest in this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mmcr.2024.100678.

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