BMC Pediatrics

CASE REPORT Open Access

Cryptococcus albidus fungemia and probable meningitis in very preterm newborn: a case report and review of the literature

Sameera Mohmmed Aljehani[1*], Tasneem Ibraheem A. Zaidan[1], Noora Obaid AlHarbi[1] and Shurooq Alharbi[1]

Abstract

Background In pediatric and neonatal age groups, infections from non-neoformans *Cryptococcus* species, notably *Cryptococcus albidus*, are rarely encountered. *C. albidus* is an emerging fungal pathogen that causes severe diseases in immunosuppressed patients; furthermore, it has rarely been reported to cause diseases in immunocompetent patients. Several cases have been described in adults who were severely immunosuppressed. Importantly, the clinical symptoms in these reported cases include fungemia, meningitis, keratitis, pulmonary and cutaneous infections. Individuals at risk include neutropenic patients, those with indwelling intravenous devices, those on prolonged steroid or antibiotic use, and those with impaired immune systems and prematurity. The susceptibility of preterm infants with low birth weight to infections, particularly fungal ones, remains a significant concern. This report presents a rare case of fungemia and meningitis due to *C. albidus* in a preterm neonate, emphasizing the clinical significance and potential implications for future treatment and management. This report aims to alert physicians of the rarity of *C. albidus* infections in pediatric patients and to review the clinical significance, pathology, treatment, and outcomes.

Case presentation We report the first case of *C. albidus* fungemia and meningitis in a very low-birth-weight, preterm infant of 31 weeks. Notably, the patient was admitted for lifesaving treatment from the Alleith Hospital due to prematurity. The patient received surfactant due to ARDS, TPN, and fluconazole prophylaxis. On day 11, features of sepsis were observed and the blood culture grew *C. albidus*, which was sensitive to liposomal agents. CSF evaluation suggested meningitis. The patient improved following a six-week treatment regimen with liposomal formulations of amphotericin B at a dosage of 5 mg/kg body weight once daily, notably administered without 5-fluorocytosine, and experienced no sequelae.

Conclusions This case report underscores the importance of early diagnosis and appropriate antifungal treatment for managing rare fungal infections in vulnerable populations, such as preterm infants. Moreover, it highlights the need for improved diagnostic platforms and comprehensive management protocols for rare pathogens in neonatal settings.

Keywords Case report, *Cryptococcus albidus*, Premature, Fungemia, Liposomal amphoterici

*Correspondence:
Sameera Mohmmed Aljehani
dr.s.m@hotmail.com
[1]Department of Pediatric-Infectious Diseases, King Abdulaziz Hospital, Almahjar Street, Jeddah 22425, Saudi Arabia

Background

Neonates, particularly premature infants with very low birth weight, are highly susceptible to infections because of their immature immune systems and exposure to maternal and environmental pathogens, often necessitating respiratory and enteral support and indwelling catheter insertion [1].

The American Academy of Pediatrics 2015 Red Book Committee on Infectious Diseases recommends using fluconazole prophylaxis to prevent serious candidiasis in very low birth weight infants in nurseries. Furthermore, prematurity, respiratory support, enteral feeding, central line infection, and use of antifungal prophylaxis are risk factors for severe and unusual infections in low-birth-weight infants [2].

Among these pathogens, fungal organisms are of particular concern due to their potential for serious infections in immunocompromised neonates. One such pathogen is *Cryptococcus*, a gram-positive, non-motile fungal yeast pathogen from the *Cryptococcaccus* family that belongs to the class *Tremellomycetes* in the division of *Basidiomycota*. *Non-neoformans Cryptococcus* species include *C. laurentii*, *C. albidus*, *C. curvatus*, *C. humicolus*, *and C. uniguttulantus* [3, 4].

The genus *Cryptococcus* is traditionally characterized by round or oval yeast cells surrounded by capsules. Substantial evidence shows that the capsule is central to *C. neoformans* survival within the host and its ability to cause disease [5].

Notably, the first reported case of human *cryptococcosis* was directly associated with pigeon excreta [6]. Furthermore, studies have shown that non-neoformans *Cryptococcus* species, specifically *C. albidus* and *C. laurentii*, are responsible for 80% of opportunistic infections [3].

This case report highlights the clinical importance of recognizing *C. albidus* as a potential, albeit rare, pathogen in very preterm infants, particularly in cases with prolonged or unexplained sepsis. Documenting and analyzing such cases are essential not only for advancing our understanding of neonatal cryptococcosis but also for refining diagnostic and therapeutic approaches to improve outcomes in this vulnerable patient group.

Case presentation

In July 2022, a male preterm infant with a gestational age of 31 weeks was admitted to the neonatal intensive care unit due to prematurity. The mother, G1P0, had no medical illness and did not receive dexamethasone. The neonate was delivered through spontaneous vaginal delivery and was born weighing 1.46 kg with Apgar scores of 7 at 1 min and 8 at 5 min. Moreover, physical examination and chest radiography revealed signs of respiratory distress syndrome. Subsequently, the infant was intubated immediately after delivery and connected to mechanical ventilation. Chest radiography confirmed grade II respiratory distress syndrome and two doses of bovine surfactant were administered. Furthermore, the infant developed hypotension, requiring inotropes. Empirical antibiotics, ampicillin, and gentamicin were started according to the Neofax dosage, pending blood culture. Oral caffeine citrate and prophylactic fluconazole were administered at 3 mg/kg/dose. Thereafter, total parenteral nutrition (TPN) was initiated, and an umbilical venous catheter was inserted.

On post-natal Day 2, the patient developed respiratory acidosis and pulmonary hemorrhage, requiring high-frequency ventilation. His complete blood count (CBC) revealed white blood cell count (WBC) of $8.3 \times 10_3$ per mm_3, hemoglobin level of 8.5 gm/dl, platelet count of 6,000/mm^3, prothrombin time of 18 s, partial thromboplastin time of 36 s, and an international normalized ratio of 1.8. Blood culture results were negative. The patient received supportive management of epinephrine via the endotracheal tube and was administered vitamin K, fresh frozen plasma, and PRBCS.

On Day 3, the echocardiogram (ECHO) showed a 2·5 mm patent ductus arterious (PDA) and pulmonary hypertension. The patient was initiated on paracetamol and sildenafil, and following improvement, antibiotics were discontinued. On Day 6, the patient was switched to conventional mechanical ventilation; the CBC was normal.

On Day 11, the patient experienced severe respiratory distress and desaturation, requiring increased ventilation. Moreover, he had low blood pressure, hypothermia, abdominal distension, leukocytosis (WBC of 17,030/mm^3, including 21% band forms), thrombocytopenia (platelet count of 96,000/ mm^3), and elevated C-reactive protein of 105 mg/L). Cerebrospinal fluid (CSF) analysis revealed pleocytosis with a total CSF WBC of 34,000/mm^3; the culture was negative. Therefore, the patient was upgraded to vancomycin and amikacin antibiotics at a dose according to the Neofax. Blood culture yielded *Staphylococcus epidermidis* from the central line, leading to the discontinuation of Amikacin and the continued use of vancomycin. On Day 12, umbilical venous catheterization was performed.

On Day 13, the patient experienced clinical deterioration, including increased abdominal girth, severe metabolic acidosis, thrombocytopenia, and anemia. Supportive management was provided through PRBCS and platelet transfusions. Blood culture yielded *Klebsiella oxytoca*, for which meropenem was initiated, and prophylactic fluconazole and vancomycin were continued. Two sets of blood culture bottles were utilized.

On Day 14, we incubated a Pediatric Plus™/F blood bottle for five days and a Mycosis IC/F blood bottle specific for the isolation of fungus for 14 days, following our

laboratory's protocol. The Pediatric Plus blood culture bottle showed positive results after 72 h, whereas the Mycosis bottle showed positive results on the sixth day of incubation. Moreover, we performed Gram staining of the positive blood culture bottles, and the stained films showed round-to-oval, yeast-like fungi; we sub-cultured the colonies on Sabouraud Dextrose agar at 37 °C and isolated growth after 48 h. Colonies were initially creamy in color but gradually darkened as they aged, and the isolated growth was identified by the VITEK®2 YST ID card (bioMérieux, Inc. St. Louis, Mo. France) as *C. albidus*. Identification was confirmed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF mass spectrometry) (Vitek MS, BioMerieux®, Marcy l'Étoile, France).

In our hospital, we do not utilize the Ligase Chain Reaction (LCR) method for the identification of *Candida albidus*, primarily because it is not available in our general hospital setting. LCR is a highly specialized molecular diagnostic technique often found in research centers or advanced diagnostic laboratories.

Instead, we rely on alternative diagnostic systems. For the identification of *Candida albidus*, we commonly use the Vitek system, which provides accurate identification of fungal species based on biochemical characteristics. To confirm the results obtained from the Vitek system, we employed MALDI-TOF mass spectrometry, a cutting-edge technology that identifies microorganisms based on protein profiles. This approach is both efficient and suitable for routine diagnostic purposes in our general hospital setting, even though more advanced molecular techniques, such as LCR, are reserved for research institutions.

On Day 16, the Infectious Diseases team was consulted, and CFS sampling was recommended, continuing vancomycin and meropenem for two weeks from the first blood culture. ECHO, eye examination, abdominal ultrasound, and administration of liposomal amphotericin B (5 mg/kg/day, once daily) were initiated. The CSF culture returned negative, ECHO showed no vegetation, the PDA was not closed, and the platelet count improved to 128,000/mm^3. Finally, abdominal ultrasonography revealed no focal lesions.

At 33 days of age, the patient was switched to conventional mechanical ventilation. A brain MRI revealed bilateral frontal and right periventricular white matter hemorrhages and a minimal subdural hemorrhage. The neurosurgeon advised the patient against any intervention. The patient received liposomal amphotericin B for six weeks and was discharged 57 days after completing the antifungal course. Follow-up appointments for one year revealed no complications, and good milestones were achieved.

Discussion

Recently, a new species of *Cryptococcus* was found to cause a fungal infection in a preterm infant with a low birth weight. In this report, the patient was a preterm infant at 31 weeks with very low birth weight who developed fungemia and meningitis due to *C. albidus*. Despite antibiotic treatment, the patient exhibited hypothermia, hypotension, and thrombocytopenia and required increased ventilatory support. However, the patient improved after receiving liposomal amphotericin B and was ultimately extubated.

Compared to term newborns, preterm premature neonates are at an increased risk of serious infection because of the passive acquisition of lower levels of maternally-derived total immunoglobulin G and specific antibodies to bacterial pathogens, poor function of neutrophils, decreased neutrophil storage pools, and immature antibody responses to pulmonary invasion and bacteremia [7]. Notably, important risk factors for this infection include an immature immune system, central line insertion, TPN, broad-spectrum antibiotics, previous use of antifungal medications while on prophylactic fluconazole, and overcrowding in the neonatal intensive care unit [8].

We identified three cases of *Cryptococcus* non-neoformans infection in pediatric patients. The first case involved a premature neonate with *C. laurentii* fungemia, who was successfully treated with amphotericin B without complications. The second case featured a 15-year-old girl with Takayasu arteritis and chronic recurrent multifocal osteomyelitis; she was also treated with amphotericin B and experienced no complications. The third case concerned a localized cutaneous *C. albidus* infection in a 14-year-old boy undergoing etanercept therapy, which resolved following a course of fluconazole [9–11].

Table 1 delineates the clinical presentation of *C. albidus* infections in adults. Specifically, twenty reported cases from 1965 to 2015 included five patients with meningitis, one with meningoencephalitis, three with pneumonia, one with peritonitis, and one with fungemia. Notably, the risk factors encompassed malignancy, human immunodeficiency virus (HIV), liver cirrhosis, diabetes mellitus, end-stage renal disease, post-transplant status, polycythemia, and prematurity.

Blood culture has long been the gold standard for diagnosing fungal infections. However, the extended time required for results—up to five days for yeasts and four weeks for molds—has historically delayed treatment and impacted outcomes. Conventional methods of identifying and detecting fungi, including microscopy, histopathology, and culture-based tests, often necessitate personnel with specialized knowledge of fungi, a resource that is sometimes limited in many institutions. Therefore,

Table 1 Cryptococcus case report data

Reference	Year	Place	Age	Sex	Underlying Disease (Immunosuppressant)
6	1965	Switzerland	75 years	M	Psychiatric history, lung cancer on autopsy
6	1968	Switzerland	73 years	F	Polycythemia vera (chemotherapy)
6	1970	Switzerland	48 years	M	None; glioblastoma of the basal ganglia developed later
7	1970	Ohio	68 years	M	None
8	1971	New York	45 years	M	Hyperthyroidism (methimazole)
9	1978	Kentucky	29 years	M	JRA, alcoholic liver disease (steroid)
10	1987	Ohio	65 years	F	AML (chemotherapy)
11	1987	Taiwan	45 years	M	Pemphigus foliaceus (steroid)
12	1991	France	38 years	M	AIDS
13	1993	Pennsylvania	37 years	M	ESRD, on HD
14	1996	Greece	47 years	F	AIDS, MDS (chemotherapy)
15	1998	Tennessee	4 years	F	ALL (chemotherapy)
16	2001	Korea	23 years	M	Kidney TPL (cyclosporine, steroid)
17	2003	Pennsylvania	51 years	M	DM, T-lymphoma, AML, SCT (chemotherapy)
18	2006	Turkey	44 years	M	Still disease (immunosuppressive therapy)
19	2011	Greece	17 days	M	Premature, 27 wk gestation
20	2012	New York	57 years	M	HCV-associated cirrhosis, hypertension, T2DM, ESRD
21	2013	Tennessee	55 years	M	Liver cirrhosis, liver TPL (sirolimus, mycophenolate mofetil, anti-thymocyte)
22	2013	China	28 years	M	AIDS
23	2015	Hungary	83 years	M	Hypertension, chronic skin rash (steroid)

non-culture methods, such as fungal antibodies, antigen detection, and DNA identification are crucial [12].

New diagnostic platforms are constantly emerging and gaining approval for use in molecular diagnostics. In diagnosing our case, we used the VITEK® ID card, which is a convenient, safe, easy-to-use disposable device that can identify up to 50 yeast varieties. Among the antifungal agents tested, amphotericin B was consistently the only agent to which *C. albidus* was susceptible, as management guidelines for this rare disease are currently lacking [13–17].

Treatment with an antifungal agent other than flucytosine was appropriate in our patient. Moreover, it is crucial to note that *C. albidus* is intrinsically resistant to echinocandins but is susceptible to posaconazole, fluconazole, voriconazole, itraconazole, and miconazole in some cases [18–21]. Notably, the optimal duration of treatment remains uncertain; however, in cases involving the central nervous system, as in our patient, treatment is typically administered for a period of six weeks.

The occurrence of organisms in a geographical area exceeding the baseline rate during a specific period is noteworthy. This sudden increase could be attributable to a single infection, such as anthrax, healthcare-associated Legionella, group A Streptococcal infection, or to multiple infections, such as those arising from food- or water-borne diseases [22]. In this context, we define it as an outbreak in the unit. Stringent infection control measures were enacted, including hand hygiene education and auditing, surveillance, surface swabs, patient isolation, care of central lines, TPN rooms, air-conditioning cleaning, and water supply monitoring.

Conclusions

Here, we report a case of *C. albidus* fungemia and meningitis in a preterm infant. Risk factors include premature birth and prolonged antibiotic use. Although the patient tested negative for HIV, the major contributing factors to fungemia included indwelling intravenous lines and TPN. Notably, very preterm infants are at high risk owing to their low weight, poor nutrition, malabsorption, low immunity, and underdeveloped barriers. Owing to the rarity of reported cases, there are no approved guidelines or standard treatments for *C. albidus*. However, we found that liposomal amphotericin B without flucytosine effectively treated our patient without complications. To prevent the spread of infection, it is crucial to implement effective infection control measures.

Abbreviations

CSF	Cerebrospinal Fluid
ECHO	Echocardiogram
HIV	Human Immunodeficiency Virus
PDA	Patent Ductus Arteriosus
PRBCS	Packed Red Blood Cells
TPN	Total Parenteral Nutrition
WBC	White Blood Cell

Acknowledgements

Dr. Hanan Al-Najjar for obtaining informed consent from the patient's father.

Author contributions

S.A. was the principal investigator who prepared the proposal and wrote the first draft of the manuscript and literature review. T.Z. was involved in the clinical management of the case, wrote the summary of the case, reviewed

the proposal, and wrote the discussion section. N.A. did the reference, review, discussion. S.A. wrote the initial outline and revised the manuscript.

Funding
This study did not receive specific grants from public, commercial, or profit funding agencies.

Data availability
Data sharing is not applicable to this article, as no datasets were generated or analyzed in the current study.

Declarations

Ethics approval and consent to participate
The child's father signed an informed consent form for the publication of this manuscript, and we obtained approval from the Institutional Review Board (IRB)–Jeddah on 24 -1-2023KACST: KSA: H-02-J-002 with approval number A01559.

Consent for publication
Written informed consent for the publication of this case report was obtained from the child's father.

Competing interests
The authors declare no competing interests.

Received: 29 September 2023 / Accepted: 20 March 2025
Published online: 02 April 2025

References

1. Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nat Rev Immunol. 2007;7:379–90.
2. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD neonatal research network. Pediatrics. 2002;110:285–91.
3. Liu XZ, Wang QM, Göker M, Groenewald M, Kachalkin AV, Lumbsch HT, et al. Towards an integrated phylogenetic classification of the tremellomycetes. Stud Mycol. 2015;81:85–147.
4. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA, Lortholary O, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. Clin Microbiol Infect. 2014;20:76–98.
5. McClelland EE, Bernhardt P, Casadevall A. Estimating the relative contributions of virulence factors for pathogenic microbes. Infect Immun. 2006;74:1500–4.
6. Jang YH, Lee SJ, Lee JH, Chae HS, Kim SH, Choe NH. Prevalence of yeast-like fungi and evaluation of several virulence factors from feral pigeons in Seoul. Korea Let App Microbiol. 2011;53:367–71.
7. Schlapbach LJ, Mattmann M, Theil S, Boillat C, Otth M, Nelle M, et al. Differential role of the lectin pathway of complement activation in susceptibility to neonatal sepsis. Clin Infect Dis. 2010;51:153–62.
8. Pagano L, Antinori A, Ammassari A, Mele L, Nosari A, Melillo L, et al. Retrospective study of candidemia in patients with hematological malignancies. Clinical features, risk factors and outcome of 76 episodes. Eur J Haematol. 1999;63:77–85.
9. Cheng MF, Chiou CC, Liu YC, Wang HZ, Hsieh KS. *Cryptococcus Laurentii* fungemia in a premature neonate. J Clin Microbiol. 2001;39:1608–11.
10. Choe YJ, Blatt DB, Yalcindag A, Geffert SF, Bobenchik AM, Michelow IC. *Cryptococcus albidus* fungemia in an immunosuppressed child: case report and systematic literature review. J Pediatr Infect Dis Soc. 2020;9:100–5.
11. Hoang JK, Burruss J. Localized cutaneous *Cryptococcus albidus* infection in a 14-year-old Boy on etanercept therapy. Pediatr Dermatol. 2007;24:285–8.
12. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71:1367–76. https://doi.org/10.1093/cid/ciz1008.
13. Espinel-Ingroff A, Stockman L, Roberts G, Pincus D, Pollack J, Marler J. Comparison of rapid yeast plus system with API 20 C system for identification of common, new, and emerging yeast pathogens. J Clin Microbiol. 1998;36:883–6.
14. Graf B, Adam T, Zill E, Göbel UB. Evaluation of the VITEK 2 system for rapid identification of yeasts and yeast-like organisms. J Clin Microbiol. 2000;38:1782–5.
15. Heelan JS, Sotomayor E, Coon K, D'Arezzo JB. Comparison of the rapid yeast plus panel with the API20C yeast system for identification of clinically significant isolates of *Candida* species. J Clin Microbiol. 1998;36:1443–5.
16. Massonet C, Van Eldere J, Vaneechoutte M, De Baere T, Verhaegen J, Lagrou K. Comparison of VITEK 2 with ITS2-fragment length polymorphism analysis for identification of yeast species. J Clin Microbiol. 2004;42:2209–11.
17. Wadlin JK, Hanko G, Stewart R, Pape J, Nachamkin I. Comparison of three commercial systems for identification of yeasts commonly isolated in the clinical microbiology laboratory. J Clin Microbiol. 1999;37:1967–70.
18. Bernal–Martinez L, Gomez–Lopez A, Castelli MV, Mesa-Arango AC, Zaragoza O, Rodriguez-Tudela JL, et al. Susceptibility profile of clinical isolates of non-*Cryptococcus neoformans*/non-*Cryptococcus Gattii Cryptococcus* species and literature review. Med Mycol. 2010;48:90–6.
19. Burnik C, Altintas ND, Ozkaya G, Serter T, Selçuk ZT, Firat P, et al. Acute respiratory distress syndrome due to *Cryptococcus albidus* pneumonia: case report and review of the literature. Med Mycol. 2007;45:469–73.
20. Loison J, Bouchara JP, Gueho E, de Gentile L, Cimon B, Chennebault JM, et al. First report of *Cryptococcus albidus* septicaemia in an HIV patient. J Infect. 1996;33:139–40.
21. Kordossis T, Avlami A, Velegraki A, Stefanou I, Georgakopoulos G, Papalambrou C, et al. First report of *Cryptococcus Laurentii* meningitis and a fatal case of *Cryptococcus albidus* cryptococcaemia in AIDS patients. Med Mycol. 1998;36:335–9.
22. Sood G, Perl TM. Outbreaks in health care settings. Infect Dis Clin North Am. 2016;30:661–87.

Publisher's note