Medical Mycology Case Reports 26 (2019) 1–4

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Multiple organ dysfunction syndrome and death secondary to *Cyberlindnera fabianii*

Mehul Desai, Bradley Nitta*, Hussain Dhanani, Svetolik Djurkovic, Shalika Katugaha

INOVA Fairfax Medical Campus, 3300 Gallows Rd, Fairfax, VA, 22042, United States

ARTICLE INFO

Keywords:
Cyberlindnera fabianii
Fungemia
Septic shock
Lymphoma
Immunosuppression

ABSTRACT

Cyberlindnera fabianii is a yeast present in soil rarely associated with invasive infection. Due to advanced diagnostic and therapeutic techniques, pathogenicity is increasingly recognized.

A 37-year-old male with B cell lymphoma on rituximab developed multiple organ dysfunction syndrome secondary to *C. fabianii* bacteremia. Specialized species identification techniques were required after failure of standard methods. Despite extracroporeal membrane oxygenation (ECMO) the patient died on day 26 after admission.

1. Introduction

Over the last decade there has been a reduction in mortality associated with B cell lymphoma due to improved recognition and treatment. Mortality is often a result of a complication of treatment or development of an infection. Fungemia carries a high risk of mortality in these immunocompromised patients [1,2]. Though less frequently pathogenic than *Candida, Cyberlindnera fabianii* is a causative organism that is increasingly being recognized. It is an ascomycetous yeast of the Saccharomycetaceae family [3]. Past names for the organism include: *Lindnera fabianii* and *Pichia fabianii* [4]. In a review of the literature, we identified nineteen published cases or case series [5–18]. These cases noted the invasive capability of *C. fabianii*, with associated sepsis often following bacterial infection.

2. Case

A 37-year-old male with no prior medical history was admitted to the medical ICU on day 0 with septic shock. The patient complained of a toothache on day −4, for which he went to an urgent care on day −1 and was started on amoxicillin clavulanate for a possible tooth abscess. He required vasopressor support and was placed on broad spectrum antimicrobial coverage with vancomycin, meropenem, clindamycin, and micafugin. The initial laboratory work-up was significant for neutropenia (ANC 70/μL), lactic acidosis, acute kidney injury, ischemic hepatitis (shock liver), and coagulopathy.

Due to encephalopathy, the patient required endotracheal intubation and mechanical ventilation on day 0. He was transitioned to veno-arterial ECMO on day 1 due to worsening septic shock with septic cardiomyopathy. Blood and sputum cultures from day 0 were positive for pan-susceptible *Escherichia coli*. The patient underwent three full volume plasma exchanges on days 1, 2, and 3 with stabilization in coagulation markers, progressive decline in vasopressor requirement, and clearance of lactate. Flow cytometry revealed a clonal expansion of B cells with a phenotype suggesting marginal zone lymphoma. Rituximab was started on day 8, along with intravenous methylprednisolone.The monoclonal B cell population was not present on repeat flow cytometry on day 20.

On day 16, while still on ECMO, the patient had increasing vasopressor requirements. Blood cultures from day 16 demonstrated yeast despite active treatment with micafungin, so voriconazole was added on day 19. Transthoracic echocardiography (TTE) on day 19 revealed a left ventricular apical thrombus. The yeast was initially identified as *Candida pelliculosa* by the Vitek system. Blood cultures were sent to a reference laboratory where *Cyberlindnera fabianii* was identified by matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) on day 24. Amphoteracin B lipid complex was added to the antifungal regimen on day 24 due to species identification and persistent fungemia despite treatment with voriconazole and micafungin. The patient continued to require increasing vasopressor support and eventually died on day 26 after transitioning to comfort care.

3. Discussion

In Table 1 we summarize the findings of 20 cases, including our

* Corresponding author.
E-mail address: bradley.nitta@inova.org (B. Nitta).

https://doi.org/10.1016/j.mmcr.2019.07.004
Received 23 May 2019; Accepted 4 July 2019
Available online 05 July 2019
2211-7539/ © 2019 The Authors. Published by Elsevier B.V. on behalf of International Society for Human and Animal Mycology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

Table 1
Comparison of prior published cases of *Cyberlindnera fabianii*.

Reference	Age/Sex	Predisposing factors	Antifungal prophylaxis	Source	Lab Tests	Diagnostic testing	Treatment	Outcome
Katagiri S, 2015	69/F	AML s/p umbilical cord blood transplantation with preconditioning therapy, mechanical ventilation, antibacterial therapy	micafungin	blood cultures	Beta D Glucan level (150)	rRNA gene amplification	amphotericin B	multi-organ failure
H.Hof, 2017	Neonate/F	ECMO, antibiotic prophylaxis, open heart surgery, peritoneal dialysis, mechanical ventilation	fluconazole	peritoneal dialysis	CRP (98)	PCR analysis	caspofungin with liposomal amphotericin B, followed by fluconazole	multi-organ failure
Minaric-Missoni, 2015	3/F	Neutropenia, Leukemia, antibacterial therapy	fluconazole	stool	CRP (24), thrombocytopenia	PCR amplification and sequence analysis	fluconazole for 5 days then inhaled amphotericin B for 14 days	survived
Minaric-Missoni, 2015	2months/M	Hydronephrosis, surgery, antibacterial therapy	none	urine	CRP (21)	PCR amplification and sequence analysis	fluconazole for 27 days, urinary catheter removal	survived
Minaric-Missoni, 2015	Neonate/F	Gastroschisis, surgery, mechanical ventilation, parenteral nutrition, antibacterial therapy	none	urine	CRP(123)	PCR amplification and sequence analysis	fluconazole for 27 days, urinary catheter removal and CVC removal	survived
Minaric-Missoni, 2015	Neonate/M	Hydronephrosis, surgery, parenteral nutrition, antibacterial therapy	none	urine	CRP (31)	PCR amplification and sequence analysis	fluconazole for 27 days, followed by caspofungin for 10 days	survived
Minaric-Missoni, 2015	Neonate/F	Intestinal atresia, surgery, parenteral nutrition, antibacterial therapy	fluconazole	blood cultures	CRP (30)	PCR amplification and sequence analysis	fluconazole for 15 days, CVC removal	survived
Minaric-Missoni, 2015	Neonate/F	Pulmonary cyst, antibacterial therapy, mechanical ventilation, parenteral nutrition	fluconazole	blood cultures	CRP (30), thrombocytopenia	PCR amplification and sequence analysis	fluconazole for 2 days, followed by caspofungin for 21 days	survived
Baghdadi J, 2015	49/F	Consumption of com ruou, ventriculoperitoneal shunt	none	CSF	WBC 7810 cells/mm3 with 66.6% polymorphonuclear cells	Sequencing of the D1/D2 region of the large subunit of 28S ribosomal RNA gene	intravenous liposomal amphotericin B 5mg/kg daily with oral flucytosine 25mg/kg QID	survived
Jindal N, 2014	5/M	Preceding antitubercular treatment, ventriculoperitoneal shunt	none	urine	300 leukocytes/mm3 with 24% neutrophils	26S rRNA gene sequencing	amphotericin B	multi organ failure
Grenouillet F, 2010	24 weeks/F	Extremely low birth weight, antibiotic therapy	none	blood cultures, pleural fluid aspirate	nonspecific	Sequencing of 26 S ribosomal DNA and internal transcribed spacer	intravenous fluconazole, followed by liposomal amphotericin B and flucytosine	multi organ failure
Bhally HS, 2006	5 week/F	Premature birth (25 and 3/7 weeks)	none	blood culture	non specific	Sequencing of D1/D2 domain of the large subunit rDNA	amphotericin B, with removal of vascular cath	survived
Yun JW, 2013	47/F	Plasma cell myeloma, lenalidomid, high dose dexamethasone	none	blood culture	pancytopenia	rRNA gene amplification	intravenous amphotericin B for 8 days, followed by caspofungin	multi organ failure
Valenza G, 2006	46/M	Mechanical ventilation, arteriovenous ECCO2R, dialysis, acute cholecystitis, antimicrobial therapy	none	blood cultures	non specific	Genomic DNA amplification	fluconazole, followed by caspofungin due to repeat growth in bronch	multi organ failure
Wu y, 2013	33 weeks/F	Premature, LBW (1760g), peripheral venous hyperalimentation, mechanical ventilation, antimicrobial therapy	none	blood cultures	non specific	26S ribosomal DNA amplification	fluconazole	survived
Hamal P, 2008	40/M	Decompressive craniotomy	fluconazole	blood cultures, and infected valve	elevated CRP	Sequencing of the ITS2 of one of the isolates	fluconazole, followed by voriconazole due to failure to clear cultures, followed by amphotericin B due to persistent fungemia	survived
Gabriel F, 2012	53/W	AKI requiring dialysis, mesenteric ischemia, antimicrobial therapy	none	oropharyngeal swab, rectal, stool cultures	elevated CRP	Sequencing of the 18S rDNA gene	IV caspofungin	survived
Lee J, 2015	87/M	Antimicrobial therapy, hemodialysis	none	blood cultures	CRP (9.65), LDH (287), leukocyte count 15,700/mm3	Sequencing of the large subunit (26S) rDNA gene	anidulafungin	multi organ failure secondary to relapse of bacterial infection
Fernández-Ruiz, 2016	48/M	Cirrhosis, autoimmune disease, corticosteroids, rituximab	none	blood cultures, CVC	non specific	PCR-based identification	caspofungin	survived

(*continued on next page*)

Table 1 (*continued*)

Reference	Age/Sex	Predisposing factors	Antifungal prophylaxis	Source	Lab Tests	Diagnostic testing	Treatment	Outcome
Our case	37/M	Antimicrobial therapy, ECMO, hemodialysis, mechanical ventilation, chemotherapy	micafungin	blood cultures	elevated vasopressor requirements	MALDI-TOF	micafungin with addition of voriconazole	multi organ failure

own, of *Cyberlindnera fabianii* following an English literature search [5–18]. *C. fabianii* does not appear to demonstrate a predilection for a specific age group. However, severe immunosuppression, major surgery, antimicrobial therapy, and low birth weight appear to be associated with increased propensity for infection. Prior antifungal therapy was present in 7 cases at the time of species identification, suggesting that treatment of *C. fabianii* requires proper identification and determination of susceptibility. Clinical presentation appears to be relatively nonspecific with fever being the most common presentation. Multiple cases noted nonspecific rises in C reactive protein and variable alterations in the manual differential. Based on review of our case and prior cases, no specific clinical or laboratory data are associated with new onset fungal infection with *C. fabianii*. In 12 of 20 cases (60%), fungemia was present. In all cases, specialized diagnostic testing was required to identify the correct organism. Therapies included all antifungal classes–azoles, echinocandins, formulations of amphotericin, and flucytosine—as well as source control when possible. Eight of the 20 patients (40%) died of multiple organ dysfunction syndrome.

Our patient had many of the risk factors identified in previous cases including immunosuppression (new diagnosis of B-cell lymphoma), neutropenia, chemotherapy (rituximab), mechanical ventilation, ECMO support, and antibiotic therapy (for preceding *E. coli* bacteremia). Classically, cellular immune mechanisms prevent cellular invasion by yeast with modest contribution from the humoral immune response [1]. There is no clear theory to explain B-cell lymphoma or rituximab, a chimeric anti-CD20 monoclonal antibody that induces B cell depletion through lysis, phagocytosis, and cell cycle arrest, would result in increased risk of rare opportunistic fungemia. Based on prior research the influence of rituximab on fungal infections remains unclear [19–21].

The presence of macro disruptive procedures (mechanical ventilation, ECMO, CRRT) seems to increase the likelihood of *Cyberlindnera* to cause systemic disease. Our patient presented with gram negative septic shock requiring salvage therapy with veno-arterial ECMO. Because of the high incidence and mortality of *Candida* sepsis, it is a strong recommendation of the Extracorporeal Life Support Organization (ELSO) Infectious Disease task force that clinicians lower the threshold for antifungal therapy for critically ill septic patients on ECMO [22]. Our case demonstrates that we should extend this vigilance to include rare non-*Candid*a yeast species that may require different therapy in this population.

Growth of *C. fabianii* on Dalmau plate culture produces spherical ovoid budding yeast cells with occasional pseudohyphae. Microscopy demonstrates spheroidal to ellipsoidal budding blastoconidia with an absence of pseudohyphae [3]. The use of routine diagnostic kits for the identification of yeast has limited ability to identify *Cyberlindnera* [9,11,23]. We suspect *Cyberlindnera* infections are often undiagnosed due to a failure to complete definitive fungal identification. In our case, the organism was initially misidentified as *Candida pelliculosa* by the Vitek system. Cultures were sent to a reference lab for further identification due to the rarity of that species. Prior cases have also demonstrated misidentification as *Candida utilis* [9]. Diagnosis of our yeast required use of MALDI-TOF MS.

C. fabianii has been described as a yeast with low virulence and a rare cause of blood stream infection and sepsis. However, our case as well as others (Table 1) have noted the organism to grow from multiple sites with a poor response to treatment with antifungal therapy. Antifungal susceptibility testing should be pursued as strains of the yeast can have varied minimum inhibitory concentrations. Prior cases also noted the rapid development of resistance in isolates following the initiation of therapy, particularly to azoles [6,16]. In our case, fungemia developed while on micafungin and persisted while on both micafungin and voriconazole. Harboring of the fungus in the intra-atrial thrombus and ECMO circuit were presumably also barriers to clearance of the blood. Past *C. fabianii* isolates demonstrated strong biofilm production [9], which likely contributed to the organism's persistence in ECMO recipients.

4. Conclusion

A high index of suspicion is necessary for rare opportunistic yeast species in immunocompromised, critically ill patients, especially in those requiring life support devices such as ECMO. *Cyberlindnera fabianii* is an emerging pathogen that can be associated with fungemia, sepsis and multiple organ dysfunction syndrome. Antibiotic therapy is a risk factor, and *C. fabianii* has the ability to breakthrough antifungal prophylaxis and empiric treatment. Given that automated identification systems can misidentify this organism as a *Candida* species, we emphasize the importance of reference testing, either with MALDI-TOF MS or fungal sequencing. Accurate identification of the yeast is essential in treatment, as *Cyberlindnera* has varying antifungal susceptibilities, which must guide therapy. It requires source control due to its resistance pattern and biofilm production. In certain patients, *C. fabianii* can be highly virulent with infection resulting in considerable mortality.

Conflict of interest

There are none.

Acknowledgements

There were no contributors to acknowledge who did not meet the criteria for authorship.

References

[1] L. Polonelli, A. Casadevall, Y. Han, F. Bernardis, T. Kirkland, R. Matthews, et al., The efficacy of acquired humoral and celular immunity in the prevention and therapy of experimental fungal infections, Med. Mycol. 38 (1) (2000) 281–292.
[2] M.G. Netea, L.A. Joosten, J.W. van der Meer, B. Kullberg, F.L. van de Veerdonk, Immune defense against Candida fungal infections, Nat. Rev. Immunol. 15 (2015) 630–642.
[3] [Internet], Mycology Online, The University of Adelaide, Adelaide, 2016 Cyberlindnera fabianii; [revised 2016 Dec; cited 2017 Dec 16];[2 screens]. Available from: https://mycology.adelaide.edu.au/descriptions/yeasts/cyberlindnera.
[4] K.C. Freel, V. Sarilar, C. Neuvéglise, H. Devillers, A. Friedrich, J. Schacherer, Genome sequence of the yeast Cyberlindnera fabianii (hansenula fabianii), Genome Announc. 2 (4) (2014) 1–2.
[5] A. Katagiri, M. Gotoh, K. Tone, D. Akahane, Y. Ito, K. Ohyashiki, et al., Fatal Cyberlindnera fabianii fungemia in a patient with mixed phenotype acute leukemia after umbilical cord blood transplantation, Int. J. Hematol. 103 (5) (2016) 592–595.
[6] H. Hof, V. Amann, C. Tauber, A. Paulun, Peritonitis in a neonate due to *Cyberlindnera fabianii*, an ascomycetic yeast, Infection 45 (6) (2017) 921–924.
[7] E. Minaric-Missoni, L. Hatvani, S. Kocsubé, C. Vágvölgyi, I. Škarić, A. Lukić-Grlić, *Cyberlindnera fabianii* in the neonatal and pediatric intensive care unit: case reports, J. Med. Microbiol. Case Rep. 2 (2015) 1–8.
[8] J. Baghdadi, P. Hemarajata, R. Humphries, T. Kelesidis, *First Report of ventriculoperitoneal shunt Infection due to* Cyberlindnera fabianii, [Internet], Case Rep. Infect. Dis. (2015 Oct) [cited 2017 Dec 16];2015:1-6. Available from: https://www.hindawi.com/journals/criid/2015/630816/.
[9] N. Jindal, S. Arora, N. Dhuria, D. Arora, *Cyberlindnera (Pichia) fabianii* infection in a neutropenic child: importance of molecular identification, J. Med. Microbiol. Case Rep. 2 (4) (2015) 1–3.
[10] F. Grenouillet, L. Millon, C. Abdourahim, G. Thiriez, O. Schulze, J. Leroy, *Pichia fabianii* fungemia in a neonate, Pediatr. Infect. Dis. J. 29 (2) (2010) 191.
[11] H.S. Bhally, S. Jain, C. Shields, N. Halsey, E. Cristofalo, W. Merz, Infection in a neonate caused by *Pichia fabianii*: importance of molecular identification, Med. Mycol. 44 (2) (2006) 185–187.
[12] J. Yun, K. Park, C. Ki, N.J. Lee, Catheter-related bloodstream infection by *Lindnera fabianii* in a neutropenic patient, J. Med. Microbiol. 62 (6) (2013) 922–925.
[13] V. Valenza, R. Valenza, J. Brederlau, M. Frosch, O. Kurzai, Identification of *Candida fabianii* as a cause of lethal septicemia, Mycoses 49 (4) (2006) 331–334.
[14] Y. Wu, J. Wang, W. Li, *Pichia fabianii* blood infection in a premature infant in China: case report, BMC Res. Notes 6 (77) (2013) 1–4.
[15] P. Hamal, J. Ostransky, M. Dendis, R. Horváth, F. Ruzicka, V. Buchta, et al., A case of endocarditis caused by the yeast *Pichia fabianii* with biofilm production and developed in vitro resistance to azoles in the course of antifungal treatment, Med. Mycol. 46 (6) (2008) 601–605.
[16] F. Gabriel, T. Noël, I. Accoceberry, *Lindnera (Pichia) fabianii* blood infection after mesenteric ischemia, Med. Mycol. 50 (3) (2012) 310–314.
[17] J.I. Lee, S. Yu, J.S. Park, E. Joo, J.H. Shin, M. Kwon, Successful treatment of fungemia caused by *Cyberlindnera fabianii* with anidulafungin: a case report, Ann. Clin. Microbiol. 18 (3) (2015) 94–97.
[18] M. Fernández-Ruiz, J. Guinea, M. Puig-Asensio, O. Zaragoza, B. Almirante, M. Cuenca-Estrella, et al., Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain, Med. Mycol. 55 (2) (2017) 125–136.
[19] N. Cooper, D.M. Arnold, The effect of rituximab on humoral and cell mediated immunity and infection in the treatment of autoimmune diseases, Br. J. Haematol. 149 (1) (2010) 3–13.
[20] M.H. van Oers, R. Klasa, R.E. Marcus, M. Wolf, E. Kimby, R.D. Gascoyne, et al., Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial, Blood 108 (10) (2006) 3295–3301.
[21] P. Rafailidis, O. Kakisi, K. Vardakas, M.E. Falagas, Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials, Cancer 109 (11) (2007) 2182–2189.
[22] G. Annich, W. Lynch, G. MacLaren, J. Wilson, R. Bartlett (Eds.), ECMO: Extracorporeal Cardiopulmonary Support in Critical Care, fourth ed., Extracorporeal Life Support, Ann Arbor, 2012.
[23] L. Svobodova, D. Bednarova, F. Ruzicka, V. Chrenkova, R. Dobi as, N. Mallatova, et al., High frequency of *Candida fabianii* among clinical isolates biochemically identified as *Candida pelliculosa* and *Candida utilis*, Mycoses 59 (4) (2016) 241–246.