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

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**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 extracorporeal 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 micafungin. 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. Amphotericin 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
| 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 | Hydrenephrosis, surgery, antibacterial therapy | none | urine | CRP (21) | PCR amplification and sequence analysis | fluconazole for 27 days, urinary catheter removal and CVC removal | survived |
| Minaric-Missoni, 2015 | Neonate/F | Gastrointest, surgery, mechanical ventilation, parenteral nutrition, antibacterial therapy | fluconazole | stool | CRP (123) | 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, antibiotic 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 corn tamao, 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 leucocytes/mm3 with 24% neutrophils | Sequencing of 26S ribosomal DNA and internal transcribed spacer | intravenous fluconazole, followed by liposomal amphotericin B and flucytosine | multi-organ failure |
| Grenouillet F, 2010 | 24 weeks/F | Extremely low birth weight, antibiotic therapy | none | blood cultures, pleural fluid aspirate | nonspecific | Sequence of 18S rDNA gene | fluconazole, by removal of vascular cath | survived |
| Bhally HS, 2006 | 5 week/F | Premature birth (25 and 3/7 weeks) | none | blood culture | non specific | Sequence of the ITS2 of rDNA gene | fluconazole, followed by removal of infected valve | 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 fluconazole, followed by amphotericin B due to repeat growth in bronch | 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 | multi-organ failure |
| Wu, 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 | IV caspofungin | 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 | survived |

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Table 1 (continued)

| Reference | Age/Sex | Predisposing factors | Source | Antifungal prophylaxis | Treatment | Lab Tests | Diagnostic testing | Outcome |
|-----------|---------|----------------------|--------|-----------------------|-----------|-----------|--------------------|---------|
|           |         |                      |        |                       | micafungin with addition of voriconazole | MALDI-TOF | required use of MALDI-TOF MS | multi organ failure |
|           |         |                      |        |                       |           |          |                    |         |

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.

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References

[1] L. Polonelli, A. Canadevall, Y. Han, F. Bernardis, T. Kirkland, R. Matthews, et al., The efficacy of acquired humoral and cellular immunity in the prevention and therapy of experimental fungal infections, Med. Mycol. 38 (1) (2000) 281–292.

[2] M.G. Netaa, L.A. Joosten, J.W. van der Meer, B. Kulberg, 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. Freels, 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. Gotob, K. Tone, D. Akahane, Y. Itou, 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. Paulsen, Peritonitis in a neonate due to Cyberlindnera fabianii, an ascomycete yeast, Infection 45 (6) (2017) 921–924.

[7] E. Minaric-Misson, L. Hatvani, S. Kocsabé, C. Vágóvölgyi, I. Škarić, A. Lukšić-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 ventriculo-peritoneal 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/crid/2015/630816/.

[9] N. Jindal, S. Arora, N. Dhubaria, 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. Bhaly, S. Jain, C. Shields, N. Haley, 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. Horvath, 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.J. 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, Am. Clin. Microbiol. 18 (3) (2015) 94–97.

[18] M. Fernández-Ruiz, J. Guinea, M. Puig-Arsenio, O. Zaragoza, B. Almirante, M. Cuena-Estrella, et al., Fungemia due to rare opportunistic yeast: 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 (1) (2007) 2182–2189.

[21] G. Annich, W. Lynch, G. MacLaren, J. Wilson, R. Bartlett (Eds.), ECMO: Extracorporeal Cardiopulmonary Support in Critical Care, fourth ed., ECMO: Extracorporeal Life Support, Ann Arbor, 2012.

[22] L. Svobodova, D. Bednarova, F. Ruzicka, V. Chrenkova, R. Dobiš, A. Lukić, A. Valenza, R. Valenza, J. Brederlau, M. Frosch, O. Kurzai, Identification of Candida fabianii in the neonatal and pediatric intensive care unit: case reports, J. Med. Microbiol. Case Rep. 2 (4) (2015) 1–6.

[23] L. Svobodova, D. Bednarova, F. Ruzicka, V. Chrenkova, R. Dobiš, A. Lukić, A. Valenza, R. Valenza, J. Brederlau, M. Frosch, O. Kurzai, Identification of Candida fabianii in the neonatal and pediatric intensive care unit: case reports, J. Med. Microbiol. Case Rep. 2 (4) (2015) 1–6.

[24] L. Svobodova, D. Bednarova, F. Ruzicka, V. Chrenkova, R. Dobiš, A. Lukić, A. Valenza, R. Valenza, J. Brederlau, M. Frosch, O. Kurzai, Identification of Candida fabianii in the neonatal and pediatric intensive care unit: case reports, J. Med. Microbiol. Case Rep. 2 (4) (2015) 1–6.

[25] L. Svobodova, D. Bednarova, F. Ruzicka, V. Chrenkova, R. Dobiš, A. Lukić, A. Valenza, R. Valenza, J. Brederlau, M. Frosch, O. Kurzai, Identification of Candida fabianii in the neonatal and pediatric intensive care unit: case reports, J. Med. Microbiol. Case Rep. 2 (4) (2015) 1–6.