Lodderomyces elongisporus: a bloodstream pathogen of greater clinical significance

K. Al-Obaid[1], S. Ahmad[2], L. Joseph[2] and Z. Khan[2]

1) *Department of Microbiology, Mubarak Al-Kabeer Hospital and* 2) *Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait*

Abstract

The true clinical significance of *Lodderomyces elongisporus* remains underestimated as a result of problems associated with its identification by the VITEK 2 yeast identification system. Here we describe a case of *L. elongisporus* primary progressive fungaemia in a woman with no known risk factors for invasive fungal infections. The isolate was identified by PCR sequencing of the internally transcribed spacer region of ribosomal DNA. Despite treatment with caspofungin, the patient died within 3 days of onset of fungaemia. Our literature review highlights this organism's emerging role as a bloodstream pathogen. A need for application of molecular methods for its accurate identification is emphasized.
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Corresponding author: Z. Khan, Department of Microbiology, Faculty of Medicine, Kuwait University, PO Box 24923, Safat 1311, Kuwait.
E-mail: zkhan@hsc.edu.kw

Introduction

Lodderomyces elongisporus was considered as a sexual state of *Candida parapsilosis* [1], and its role in human infection was unknown until recently. Sequencing of the ribosomal RNA gene revealed that *L. elongisporus* represents a distinct species [2]. The aetiologic role of *L. elongisporus* was subsequently established in human infections [3]. Of ten clinical isolates identified as *L. elongisporus,* eight originated from Mexico, while one each came from China and Malaysia [4]. These isolates were previously misidentified as *C. parapsilosis* by the VITEK 2 yeast identification system. *L. elongisporus* has been isolated from bloodstream and from the catheter tip of a case of suspected fungaemia patient in Kuwait [3–5].

Here we describe a case of primary fungaemia by *L. elongisporus* that progressed rapidly with fatal outcome despite prompt initiation of treatment with caspofungin.

Case summary

A 71-year-old woman with a history of hypertension, ischaemic heart disease and peripheral vascular disease was brought to emergency room in an unconscious state. Head computed tomographic scan revealed a stroke. On day 2, her condition deteriorated rapidly, requiring inotropic support. She developed septic shock, as indicated by elevated levels of inflammatory markers (erythrocyte sedimentation rate, 70 mm/h; C-reactive protein, 78 mg/L). Blood obtained at this time grew a yeast in both aerobic and anaerobic BacT/ALERT culture bottles. Pending identification, caspofungin was administered immediately, but she died on day 3 of her hospital stay.

The yeast isolate (Kw553/18) was identified as *C. parapsilosis* by the VITEK 2 yeast identification system (bioMérieux, Marcy l'Etoile, France). The isolate was referred to the Mycology Reference Laboratory for further characterization. On CHROMagar Candida (CHROMagar, Paris, France), it produced turquoise blue colonies (Fig. 1) instead of cream-coloured colonies with a pinkish shade, which is characteristic of *C. parapsilosis,* thus prompting further identification. On acetate ascospore agar after 7 days of incubation at 25°C, the isolate formed long ellipsoidal-shaped ascospores (Fig. 2), suggesting its identity as *L. elongisporus*. The internally transcribed spacer region of ribosomal DNA was amplified and sequenced as described previously [6,7]. DNA sequence data comparisons of Kw553/18 (European Molecular Biology Laboratory accession no. LS482924) showed complete (100%) identity with the corresponding sequence from *L. elongisporus* type strain (ATCC 11503) but only 83% identity with the sequence from reference *C. parapsilosis* strain (ATCC 22019) [8]. The findings also suggested that *Candida* species isolates forming turquoise blue colonies on CHROMagar Candida and producing ascospores on acetate ascospore agar can be presumptively identified as *L. elongisporus* for laboratories where molecular identification methods are not available.

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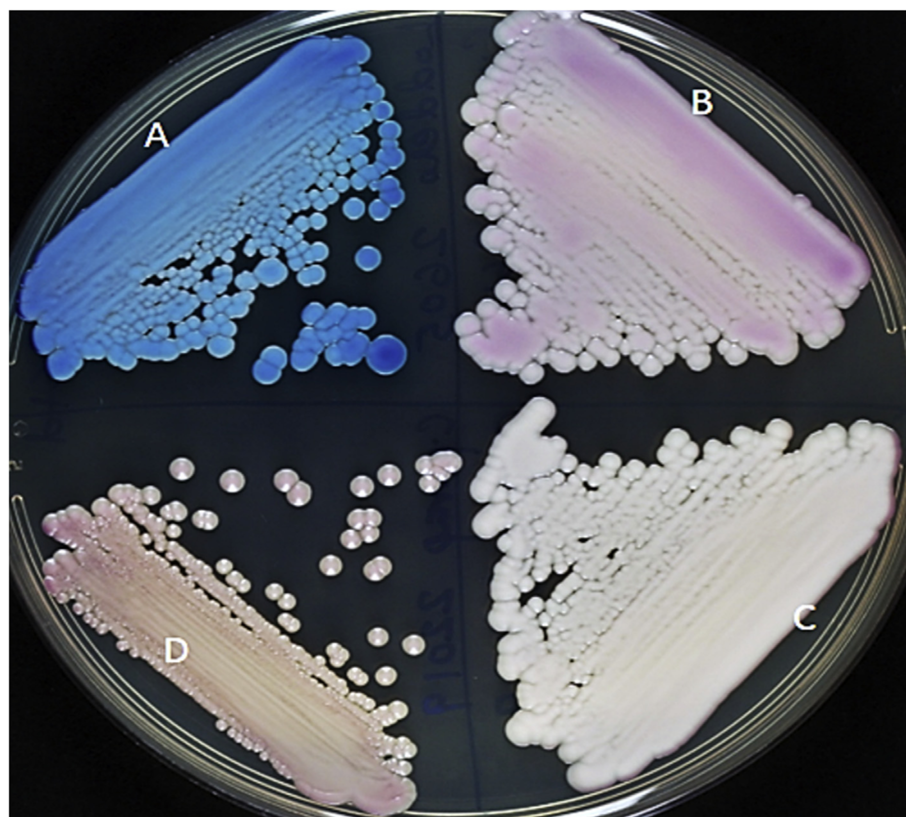

FIG. 1. Colony characteristics of *Lodderomyces elongisporus* (Kw553/18) (A), *Candida metappsilosis* (B), *C. orthopsilosis* (C) and *C. parapsilosis* (D) on CHROMagar Candida. Note turquoise blue colonies of *L. elongisporus*.

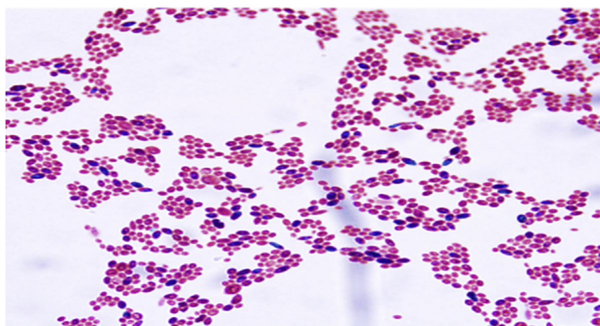

FIG. 2. Ellipsoidal to elongate ascospores (green) of *Lodderomyces elongisporus* produced on acetate ascospore agar and stained with Schaeffer-Fulton stain. Original magnification, ×1000.

Antifungal susceptibility was determined by Etest (bioMérieux) on RPMI 1640 medium supplemented with 2% glucose, as described previously [9]. MIC values (μg/mL) were as follows: amphotericin B, 0.012; fluconazole, 0.125; voriconazole, 0.004; posaconazole, 0.003; itraconazole, 0.008; flucytosine, 0.064; caspofungin, 0.064; micafungin, 0.003.

Results

The unusual aspect of our case is that there were no apparent risk factors in the patient when fungaemia was diagnosed. However, she had a history of heart disease and had also experienced a stroke. She was not receiving any antibiotics; nor had any central lines been emplaced. She was hospitalized earlier for lower limb ischaemia due to peripheral vascular disease, but she was discharged 2 weeks before the current episode. It is not clear how she developed fungaemia as a result of this unusual yeast in the absence of any known risk factors. However, the possibility of inoculation of the yeast from the skin or translocation from the gastrointestinal tract cannot be ruled out.

Although *L. elongisporus* is a recognized bloodstream pathogen [3], little is known about its virulence attributes or its environmental niche. Like other opportunistic yeast pathogens, this species is also capable of causing diverse clinical conditions, including endocarditis. The species has a global prevalence: it has been isolated from patients in distant geographic regions, including Mexico, Malaysia and China [3], Australia [10], the

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TABLE 1. Summary of salient findings of published cases of *Lodderomyces elongisporus* fungaemia

Case no.	Study	Country	Age/sex	Comorbidities or risk factors	Identification method
1	Daveson 2012 [10]	Australia	30/M	Endocarditis, osteomyelitis and brain embolic lesions; intravenous drug user	• Blue-green colonies on CHROMagar (BD Diagnostics). • ITS region sequence analysis.
2[a]	Ahmad 2013 [5]	Kuwait	63/M	Cardiovascular attack, vascular catheter	• Turquoise blue colonies on CHROMagar Candida (Becton Dickinson). • Identified as *Candida parapsilosis* by VITEK 2 yeast identification system (bioMérieux). • PCR sequencing of ITS region of rDNA.
3	Taj-Aldeen 2014 [11]	Qatar	22/M	Trauma	• MALDI-TOF MS. • Sequence analysis of ITS region and D1–D2 domains of rDNA.
4	Hatanaka 2016 [12]	Japan	39/M	Thoracoabdominal aortic replacement complicated with aortoesophageal fistula, catheter	• Dark green colonies *Candida* agar medium. • Identified as *C. parapsilosis* by VITEK 2 system (bioMérieux). • Sequence analysis of ITS region and D1–D2 domains of rDNA.
5	Fernández-Ruiz 2017 [13]	Spain	79/M	COPD, diabetes mellitus, ESRD	• Sequencing ITS region of rDNA.
6	Lee 2018 [14]	Korea	56/F	Lung cancer, receiving immunosuppressive agents, vascular catheter	• Turquoise blue colony on CHROMagar. • *Candida* medium. • VITEK 2 YST ID (bioMérieux) and API 20C AUX (bioMérieux) system identified it as *C. parapsilosis.* • MALDI-TOF MS (Bruker Daltonics) analysis indicated likely identification of *L. elongisporus* (score value = 1.79). • Sequence analysis of ITS region of rDNA.
7	Present case	Kuwait	71/F	Hypertension, ischaemic heart disease, peripheral vascular disease	• Blue colonies in CHROMagar Candida. • Identified as *C. parapsilosis* in VITEK 2 yeast identification system (bioMérieux). • PCR sequencing of ITS region of rDNA.

COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ITS, internally transcribed spacer; MALDI-TOF MS, matrix-assisted desorption ionization–time of flight mass spectrometry; rDNA, recombinant DNA.
[a]In case 2, *L. elongisporus* was isolated from catheter tip culture.

Middle East [5,11], Japan [12], Spain [13] and Korea [14] (Tables 1 and 2).

The salient findings of seven individual case reports of *L. elongisporus* fungaemia are summarized in Tables 1 and 2. All patients had associated comorbidities and/or risk factors including an intravenous drug user (patient 1). Four (57.5%) of seven patients died even though six patients were treated with antifungal drugs. Because the number of patients is small, it is difficult to assess the impact of antifungal therapy on the outcome. It is also not clear if use of echinocandins (caspofungin in four patients and micafungin in one patient) was an appropriate therapy for *L. elongisporus* fungaemia because three of five patients died.

Discussion

Data on antifungal susceptibility of *L. elongisporus* are scanty, and no susceptibility breakpoints are available. *C. parapsilosis* complex members, to which *L. elongisporus* is closely related, generally show reduced susceptibility to echinocandins [15]. The *in vitro* MIC values for antifungal drugs for *L. elongisporus* isolates were within the susceptible range (Table 3) [3,5,10–14,16]. Although echinocandins have lower *in vitro* activity against *C. parapsilosis* complex members to which *L. elongisporus* is closely related, the current Infectious Disease Society of America guidelines still favour therapeutic use of echinocandins for the treatment of candidaemia caused by *C. parapsilosis* [17].

Uncommon yeast pathogens are often misidentified as a result of limitations of the currently available commercial yeast identification systems, such as VITEK 2, which identify *C. parapsilosis* complex but do not distinguish *C. parapsilosis, C. orthopsilosis, C. metapsilosis* and *L. elongisporus* [18]. A retrospective characterization of 380 *C. parapsilosis* complex isolates available in the Mycology Reference Laboratory culture collection and previously speciated by VITEK 2 by a multiplex PCR assay [19] that simultaneously detected *C. parapsilosis, C. orthopsilosis, C. metapsilosis* and *L. elongisporus* identified three *L. elongisporus* isolates. One isolate was obtained from sputum of a cancer patient (isolate Kw2486/06); another isolate (Kw554/08) was recovered from the catheter tip of a patient with fungaemia [5]; and a third isolate (Kw3047/14) was isolated from the bloodstream of a cancer patient. However, clinical details of the two cancer patients were not available. Recently matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has also been used for the identification of *L. elongisporus* [20].

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TABLE 2. Treatment and outcome of *Lodderomyces elongisporus* fungaemia

Case no.	Study	Treatment	Outcome
1	Daveson 2012 [10]	Caspofungin before cardiac surgery, then amphotericin B plus flucytosine followed by voriconazole	Survived
2[a]	Ahmad 2013 [5]	Fluconazole	Survived
3	Taj-Aldeen 2014 [11]	Caspofungin, fluconazole	Died
4	Hatanaka 2016 [12]	Micafungin	Survived
5	Fernández-Ruiz 2017 [13]	Caspofungin 3 days	Died
6	Lee 2018 [14]	Not provided	Died before removal of indwelling catheter or antifungal treatment
7	Present case	Caspofungin (one dose)	Died

[a]In case 2, L elongisporus was isolated from catheter tip culture.

TABLE 3. Antifungal susceptibility profile of *Lodderomyces elongisporus* isolates

			MIC (μg/mL) of:										
Study	No. of isolate	Method	AP	5-FC	FL	IT	KE	VO	POS	ISA	CS	AND	MYC
Lockhart 2008 [3]	9	BMD, CLSI	0.37–0.75	NA	0.12–0.025	NA	NA	NA	NA	NA	0.015–0.03	0.015–0.12	0.015–0.03
Tay 2009 [16]	1	Etest	0.012	NA	0.125	0.047	0.003	0.004	NA	NA	NA	NA	NA
Daveson 2012 [10]	1	NA	0.25	0.06	≤0.125	0.06	≤0.008	≤0.008	0.03	NA	0.03	NA	NA
Ahmad 2013 [5]	1	Etest	NA	0.094	0.32	NA	NA	0.002	0.023	NA	0.094	NA	NA
Taj-Aldeen 2014 [11]	1	BMD, CLSI	0.5	NA	0.25	0.031	NA	<0.016	0.063	<0.016	0.5	0.016	NA
Hatanaka 2016 [12]	1	BMD, CLSI	0.25	0.5	0.5	0.25	NA	0.015	NA	NA	NA	NA	0.015
Fernández-Ruiz 2017 [13]	1	BMD, CLSI	0.031		0.125	NA	NA	0.0017	0.007	NA	NA	0.015	0.015
Lee 2018 [14]	1	ATB Fungus 3	0.25	1.00	1.00	NA	NA	0.12	NA	NA	0.25	NA	0.06
Present case	1	Etest	0.012	0.064	0.125	0.008	0.003	0.004	0.003	NA	0.064	0.008	0.032

5-FC, 5-flurocytosin; AND, anidulafungin; AP, amphotericin; BMD, broth microdilution; CLSI, Clinical and Laboratory Standards Institute; CS, caspofungin; FL, fluconazole; ISA, isavuconazole; IT, itraconazole; KE, ketoconazole; MYC, micafungin; NA, not available; POS, posaconazole; VO, voriconazole.

Rare yeast species often exhibit reduced susceptibility to one or more commonly used antifungal agents [18]. A number of factors have been attributed to their increased occurrence, such as prolonged survival of seriously ill patients admitted in intensive care units, administration of multiple broad-spectrum antibiotics, dependence on life support systems and extended use of intravascular catheters [21]. It is also possible that these relatively less susceptible yeasts take advantage of the selection pressure created by prophylactic and therapeutic use of antifungal agents, resulting in increased colonization and invasive infection [18,21]. Perhaps a delay in accurate identification and a lack of experience in the management of such rare yeast infections pose diagnostic and therapeutic challenges with consequently higher mortality rates.

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Conflict of interest

None declared.

References

[1] Hamajima K, Nishikawa A, Shinoda T, Fukazawa Y. Deoxyribonucleic acid base composition and its homology between two forms of *Candida parapsilosis* and *Lodderomyces elongisporus*. J Gen Appl Microbiol 1987;33:299–302.

[2] James SA, Collins MD, Roberts IN. The genetic relationship of *Lodderomyces elongisporus* to other ascomycete yeast species as revealed by small-subunit rRNA gene sequences. Lett Appl Microbiol 1994;19:311.

[3] Lockhart SR, Messer SA, Pfaller MA, Diekema DJ. *Lodderomyces elongisporus* masquerading as *Candida parapsilosis* as a cause of bloodstream infections. J Clin Microbiol 2008;46:374–6.

[4] Lockhart SR, Messer SA, Pfaller MA, Diekema DJ. Geographic distribution and antifungal susceptibility of the newly described species *Candida orthopsilosis* and *Candida metapsilosis* in comparison to the closely related species *Candida parapsilosis*. J Clin Microbiol 2008;46:2659–64.

[5] Ahmad S, Khan ZU, Johny M, Ashour NM, Al-Tourah WH, Joseph L, et al. Isolation of *Lodderomyces elongisporus* from the catheter tip of a fungemia patient in the Middle East. Case Rep Med 2013;2013:560406.

[6] Khan ZU, Ahmad S, Mokaddas E, Chandy R, Cano J, Guarro J. *Actinomucor elegans* var. *kuwaitiensis* isolated from the wound of a diabetic patient. Antonie van Leeuwoenhoek 2008;94:343–52.

[7] Khan ZU, Ahmad S, Hagen F, Fell JW, Kowshik T, Chandy R, et al. *Cryptococcus randhawai* sp. nov., a novel anamorphic basidiomycetous yeast isolated from tree trunk hollow of *Ficus religiosa* (peepal tree) from New Delhi, India. Antonie Van Leeuwenhoek 2010;97:253–9.

[8] Schoch CL, Seifert KA, Huhndorf S, Robert V, Spouge JL, Levesque CA, et al. Nuclear ribosomal internal transcribed spacer

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(ITS) region as a universal DNA barcode marker for fungi. Proc Natl Acad Sci USA 2012;109:6241–6.

[9] Asadzadeh M, Al-Sweih NA, Ahmad S, Khan ZU. Antifungal susceptibility of clinical *Candida parapsilosis* isolates in Kuwait. Mycoses 2008;51:318–23.

[10] Daveson KL, Woods ML. *Lodderomyces elongisporus* endocarditis in an intravenous drug user: a new entity in fungal endocarditis. J Med Microbiol 2012;61:1338–44.

[11] Taj-Aldeen SJ, AbdulWahab A, Kolecka A, Deshmukh A, Meis JF, Boekhout T. Uncommon opportunistic yeast bloodstream infections from Qatar. Med Mycol 2014;52:552–6.

[12] Hatanaka S, Nakamura I, Fukushima S, Ohkusu K, Matsumoto T. Catheter-related bloodstream infection due to *Lodderomyces elongisporus*. Jpn J Infect Dis 2016;69:520–2.

[13] Fernández-Ruiz M, Guinea J, Puig-Asensio M, Zaragoza Ó, Almirante B, Cuenca-Estrella M, et al., CANDIPOP Project, GEI H-GEMICOMED (SEIMC), REIPI. Fungemia due to rare opportunistic yeasts: data from a population-based surveillance in Spain. Med Mycol 2017;55:125–36.

[14] Lee HY, Kim SJ, Kim D, Jang J, Sung H, Kim MN, et al. Catheter-related bloodstream infection due to *Lodderomyces elongisporus* in a patient with lung cancer. Ann Lab Med 2018;38:182–4.

[15] Sanguinetti M, Posteraro B, Lass-Flörl C. Antifungal drug resistance among *Candida* species: mechanisms and clinical impact. Mycoses 2015;58(Suppl. 2):2–13.

[16] Tay ST, Na SL, Chong J. Molecular differentiation and antifungal susceptibilities of *Candida parapsilosis* isolated from patients with bloodstream infections. Med Microbiol 2009;58(Pt 2):185–91.

[17] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–50.

[18] Khan Z, Ahmad S. *Candida auris*: an emerging multidrug-resistant pathogen of global significance. Clin Med Res Pract 2017;7:240–8.

[19] Asadzadeh M, Ahmad S, Hagen F, Meis JF, Al-Sweih N, Khan Z. Simple, low-cost detection of *Candida parapsilosis* complex isolates and molecular fingerprinting of *Candida orthopsilosis* strains in Kuwait by ITS region sequencing and amplified fragment length polymorphism analysis. PLoS One 2015;10, e0142880.

[20] De Carolis E, Hensgens LA, Vella A, Posteraro B, Sanguinetti M, Senesi S, et al. Identification and typing of the *Candida parapsilosis* complex: MALDI-TOF MS vs. AFLP. Med Mycol 2014;52:123–30.

[21] Miceli MH, Díaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infect Dis 2011;11:142–51.

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