CASE REPORT

Fatal *Lodderomyces elongisporus* Fungaemia in COVID-19 Patient

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ABSTRACT

Lodderomyces elongisporus, an ascomycetous yeast, is often misidentified as *Candida parapsilosis* due to its physiologic similarity. Compared to *Candida parapsilosis* complex, *L. elongisporus* is still inferior in regard to incidence and virulence. We report a case of *L. elongisporus* fungaemia in a patient with diabetic ketoacidosis (DKA) precipitated by COVID-19 category 5 infection. A 52-year-old diabetic and hypertensive lady was brought in for fever, cough and lethargy for four days, with sudden onset of dyspnoea. Upon arrival, she was febrile, and in metabolic ketoacidosis. Her lung auscultation was clear. SARS-CoV-2 RNA was detected via real-time polymerase chain reaction (RT-PCR). Her blood culture grew *L. elongisporus*, identified via matrix-assisted laser desorption/ionization time of flight (MALDI-TOF). Although treated with intravenous (IV) amphotericin B for four days, she succumbed on the sixth day of admission. Accurate identification of this yeast, especially in differentiating it with *Candida parapsilosis* complex, remains a diagnostic challenge for routine diagnostic laboratories. MALDI-TOF offers a reliable alternative for accurate and prompt diagnosis. Co-infections with COVID-19 have never been recorded worldwide. We highlight the first case of *L. elongisporus* isolation co-existing with SARS-CoV-2 infection during this pandemic.
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INTRODUCTION

Invasive fungal infections aggravate one fifth of SARS-CoV-2 patients, afflicting them with 60% of mortality rate (1). This increased incidence rate and fatality outcome are attributed to immunocompromised state from host comorbidities, viral immunological response and treatment. *Lodderomyces elongisporus* is an ascomycetous yeast, often to be confused with *Candida parapsilosis* due to its physiologic similarity. Out of 542 laboratory-identified *C. parapsilosis* isolates received in an international research, 1.8% of them were misidentified and found to be *L. elongisporus* (2). Compared to the more common *Candida parapsilosis* complex, *L. elongisporus* is still less virulent and cause low incidence of infection. This rare fungus has been increasing in clinical significance, especially in catheter-related infections. However, co-infections with COVID-19 have never been reported globally. We describe a rare case of *L. elongisporus* fungaemia in Malaysia, isolated in a SARS-CoV-2 positive patient during this Coronavirus Disease 2019 (COVID-19) pandemic.

CASE REPORT

Mrs. C, a 52-year-old Siamese lady is a known case of uncontrolled diabetes mellitus and hypertension defaulting follow-up. She was brought to a district hospital via ambulance for fever, cough, anorexia and lethargy for the past four days, associated with dyspnoea for one day. Upon arrival, she was tachycardic (135 beats per minute) with low grade fever (T 37.5^{o}C), tachypnoeic (respiratory rate 35/min) and her oxygen saturation was 68% under high flow mask oxygen 15L/min. There were no adventitious lung sounds. Cardiovascular and abdominal examination were both unremarkable. Capillary blood glucose was found to be high (24.1 mmol/L) with ketonaemia (3.8 mmol/L). Full blood count demonstrated leucocytosis (11.2 x 10^3/µL) with normal haemoglobin (14.1 g/dL) and platelet counts (336 x 10^9/µL). Her acute phase reactants such as C-reactive protein, procalcitonin, ferritin and blood lactate levels were elevated, with values of 96 mg/L, 1.55 ng/mL,

1278 µg/L and 3.4 mmol/L, respectively. Chest radiograph portrayed heterogenous opacity of bilateral lung fields. Her naso-oropharyngeal swab RT-PCR detected SARS-CoV-2 virus E, N and RdRP genes with CT values of 27.06, 25.98 and 28.06, respectively.

Treated as DKA precipitated by COVID-19, she required mechanical ventilation, central line access and urinary catheter. She was stabilised as per DKA protocol. A percutaneous blood was drawn and sent to the laboratory for bacterial culture and susceptibility testing. Intravenous dexamethasone and tocilizumab was given for her COVID-19, with IV amoxicillin-clavulanic acid was started for suspected community-acquired pneumonia.

After thirty-nine hours incubation, the blood culture BACTEC® system signalled positivity. Gram stain showed ellipsoidal budding yeast cells and was immediately notified to the attending clinicians (Fig. 1). Upon gram stain result notification, she was treated empirically with IV amphotericin B 50mg daily. Culture grew pure white cheesy colonies, and

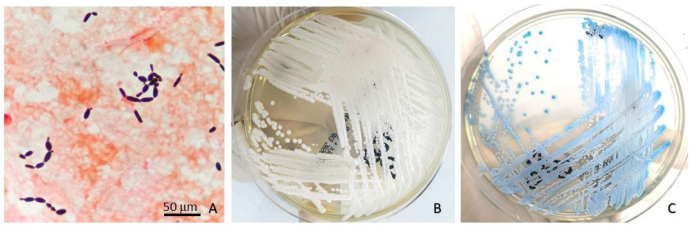

Figure 1 : Gram-positive budding yeast cells (A) and colonies on (B) Sabouraud dextrose agar (SDA) and (C) CHROMagar Candida. Note the distinct turquoise blue colonies seen on CHROMagar.

subculture of the isolate on CHROMagar Candida agar (Isolac®, Isolab Sdn Bhd, Selangor, Malaysia) yielded turquoise blue colonies. Germ tube test did not exhibit hyphal extension.

The colony was identified as *Lodderomyces elongisporus* via MALDI-TOF MS (Bruker Daltonics, Germany) using direct transfer method, with a log[score] value of 1.89. Susceptibility testing was subsequently carried out (Vitek 2, bioMerieux System, North Carolina, USA) demonstrating low minimum inhibitory concentrations (MICs) towards amphotericin B, fluconazole, caspofungin, voriconazole, micafungin and flucytosine of <0.25 µg/mL, 0.5 µg/mL, <0.12 µg/mL, <0.12 µg/mL, <0.06 µg/mL and <1 µg/mL, respectively. The result was fully released by day 3 of admission. Meanwhile, her urine and tracheal aspirate cultures were negative for both bacterial and fungal growth.

Unfortunately, her sepsis was complicated with type 2 myocardial infarction. Since day 2 of admission, her electrocardiogram demonstrated global T wave inversion, and Troponin I was raised (3.6 ng/mL). She was also treated for possible pulmonary embolism justified by raised D-dimer levels (>7.65 µg/mL). She was planned for computed tomography pulmonary angiography, echocardiography and fundoscopy. However, she succumbed on her sixth day of admission.

DISCUSSION

Lodderomyces elongisporus was first recovered by Recca and Mrak in 1952 from Californian citrus concentrate. It was initially named as *Saccharomyces elongasporus* due to its large, distinctive, elongated ascospores formation. However, due to its morphological and physiological features too distinctive and anascogenous (imperfect) to belong with the other members of Saccharomyces genera, it was deemed justified to give it a new generic classification. Thus, to honour Dr. Jacomina Lodder of Delft's outstanding contributions in yeast taxonomy, a new genus name Lodderomyces was proposed in 1966.

Advancement in molecular diagnostics have brought it nearer to the Candida species. Although extremely high rate of DNA homology percentages prompted researchers to propose it as the teleomorph (sexual form) of *C. parapsilosis*, this was negated by James and colleagues' 18S rRNA gene sequencing, but supports the close-relatedness of *L. elongisporus* genes to *C. parapsilosis* sensu stricto, *C. tropicalis* and *C. albicans*.

Because of its physiologic resemblance to *C. parapsilosis*, this species may have gone undiscovered in clinical samples since its identification. During Lockhart and colleagues' research on international collection of *C. parapsilosis* isolates, two percent of the isolates turned out to be *L. elongisporus* due to their distinctive colour on chromogenic media and failure of BanI-digested SADH fragment amplification screening to identify them as *C. parapsilosis*, C. orthopsilosis, or C. metapsilosis (2). In exception to Lockhart et al, most author has yet to classify it as the fourth member of *Candida parapsilosis* complex (2).

This is the fourth recorded case of *L. elongisporus* fungaemia in Malaysia (2). However, co-infections with COVID-19 have never been reported worldwide. This case highlights the rarity of this ascomycetous yeast and its first isolation from a patient with SARS-CoV-2 infection.

More data is needed to delineate risk factors for *L. elongisporus* infection. Lockhart and colleagues concluded no gender predominance, but an age preponderance of patients older than 40 years old is demonstrated (2), which corresponds with this case. Apart from her diabetic status and SARS-CoV-2

infection, the patient has had no other risk factors for disseminated fungal infection. The patient's blood culture was drawn upon hospital admission, prior to central venous catheter and urinary catheter insertion. Urine and tracheal aspirate cultures were also negative. The patient also had no history of prior hospitalization. These factors reduce the likelihood of nosocomial origin, putting our case out of the norm (3).

Accurate identification of this yeast remains a diagnostic challenge for routine diagnostic laboratories with limited resources. Similar to *Candida parapsilosis* complex members, *L. elongisporus* grew white to cream-coloured cheesy-like colonies on Sabouraud dextrose agar with negative germ tube test. API® 20C AUX, ID 32 C and Vitek 2 (bioMèrieux) yeast identification kits and systems do not have specific biochemical testing parameter for it, thus will only identify it as *Candida parapsilosis*. Chromogenic media can impart distinguishing turquoise-blue colonies, but colour recognition is subjective. Although useful in resource-limited settings, relying solely on chromogenic agar may result in confusion with the light blue *Candida auris* and metallic blue *Candida tropicalis*. The only distinguishing feature between *L. elongisporus* and members of *Candida parapsilosis* complex is the long, ellipsoidal-shaped ascospores demonstrated on cornmeal agar and malt extract agar cultures, which unfortunately, may not be readily available in many clinical diagnostic laboratories.

In addition to the specialized agar, most literature recommend molecular identification for *L. elongisporus* from *Candida parapsilosis* complex species. MALDI-TOF is reliable in identifying uncommon fungal pathogens in a timely manner, like was shown in this case (4). No further identification method was performed.

The breakpoint values for *L. elongisporus* MICs have yet to be established, and there is no specific clinical guideline in treating this fungal pathogen. Although *L. elongisporus* is known to exhibit lower virulence and are susceptible to most antifungals with lower MICs compared to *Candida parapsilosis* complex, its associated mortality still exceeds 50% (3), which is exorbitant as compared to the 28.5% average mortality for *C. parapsilosis* sensu stricto (5). More data is still needed to accurately predict the mortality rate associated with *L. elongisporus*.

CONCLUSION

Lodderomyces elongisporus is associated with low virulence but high mortality. A high index of suspicion amongst risk groups and early diagnosis of fungaemia are important factors to reduce the fatality due to its susceptibility to all classes of antifungal agents.

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REFERENCES

1. Szabo BG, Lakatos B, Bobek I, Szabo E, Szlavik J, Valyi-Nagy I. Invasive fungal infections among critically ill adult COVID-19 patients : First experiences from the national centre in Hungary Istv a. J Med Mycol. 2021;31:0–6.
2. 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(1):374–6.
3. Al-Obaid K, Ahmad S, Joseph L, Khan Z. *Lodderomyces elongisporus* : a bloodstream pathogen of greater clinical significance. New Microbes New Infect [Internet]. 2018;26:20–4. Available from: https://doi.org/10.1016/j.nmni.2018.07.004
4. Taj-aldeen SJ, Abdulwahab A, Kolecka A. Uncommon opportunistic yeast bloodstream infections from Qatar Uncommon opportunistic yeast bloodstream infections from Qatar. Med Mycol [Internet]. 2014;52(June):549–53. Available from: https://www.researchgate.net/publication/263207089_Uncommon_opportunistic_yeast_bloodstream_infections_from_Qatar
5. Trofa D, Ga A, Nosanchuk JD. *Candida parapsilosis*, an Emerging Fungal Pathogen. Clin Microbiol Rev. 2008;21(4):606–25.