CASE REPORT

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Diagnostic Challenges in Non-albicans Candida Bloodstream Infection in an Immunocompromised Patient: A Case Report

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ABSTRACT

Introduction: Candidemia has increased in recent years, leading to prolonged hospital stay, increased healthcare costs, and high mortality. Patients with underlying conditions such as malignancy and those requiring invasive medical devices are at higher risk of Candida bloodstream infection. Therefore, this study aims to describe a rare case of non-albicans Candida bloodstream infection in an immunocompromised patient, with emphasis on diagnostic challenges and clinical implications of discordant laboratory identification in guiding appropriate management.

Case Description: A 48-year-old female with cervical cancer undergoing chemotherapy and hemodialysis via a right-thigh double-lumen catheter presented to the emergency department with prolonged vaginal bleeding, oliguria, nausea, and significant weight loss. Laboratory findings revealed leukocytosis and renal impairment. She received a combination of ceftazidime, moxifloxacin, and metronidazole in the ICU. The patient had multiple invasive devices, including intravenous catheters, parenteral nutrition, and urinary catheters. Blood culture performed on day 15 of hospitalisation identified *Candida lipolytica*, which was sensitive to voriconazole, amphotericin B, and flucytosine. Moreover, PCR and phylogenetic sequencing were performed to ensure accurate species identification. Despite the final identification and clinical management efforts, the patient's clinical condition continued to deteriorate, and she eventually succumbed after three weeks of hospitalisation.

Conclusion: This case highlights a rare non-albicans Candida bloodstream infection in an immunocompromised patient, emphasising the diagnostic challenges associated with accurate species identification. A stepwise diagnostic approach with culture, proteomic, and molecular confirmation, including PCR and phylogenetic analysis, is essential to ensure accurate identification and optimal clinical management.

Keywords: bloodstream infection, non-albicans Candida, candidemia, immunocompromised.
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INTRODUCTION

Candidemia is an infection of Candida species in the bloodstream that can be detected by blood culture.[1–3] The incidence of candidemia increases every year, and candidemia causes high mortality rates, increases the length of stay, and costs.[4] More than 90% of candidemia cases are caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*.[5–7] There has been an increase in cases of infection by non- *C. albicans* species, especially *C. glabrata* and *C. parapsilosis*.[8] Several *Candida* species, such as *C. guilliermondii, C. pelliculosa, C. lypolytica, and C. dubliniensis,* have also been reported as the causes of candidemia.[3] Critically, non-*albicans Candida* species have been associated with higher mortality and greater antifungal drug resistance compared to *C. albicans* infections.[9] This epidemiological transition carries profound therapeutic implications, as different *Candida* species exhibit inherently variable susceptibility profiles to antifungal agents, necessitating accurate species-level identification to guide appropriate clinical management.[10,11] Risk factors associated with candidemia, such as malignancy, neutropenia, length of stay in ICU, candida colonisation, diabetes, renal failure, hemodialysis, use of broad-spectrum antibiotics, use of CVC, parenteral nutrition, and immunosuppression.[2,6,12–16]

Laboratory diagnosis of candidemia, by which blood culture is used as a diagnostic tool for candidemia, fails to detect up to 65% of cases. This is because the clinical picture of candidemia is not specific, so empirical therapy is given before the blood culture results are known.[17] Commercial yeast identification systems, such as Vitek 2, are less satisfactory at identifying certain *Candida* species, including *C. tropicalis*, and the overall misidentification rate for rare species by phenotypic identification has been reported to be as high as 20.0%, compared to only 2.2% for the four most common *Candida* species.[18] Matrix-assisted laser desorption ionisation–time

of flight mass spectrometry (MALDI-TOF MS) has emerged as a rapid, reliable, and cost-effective alternative for yeast identification, largely supplanting traditional phenotypic methods in many clinical microbiology laboratories.[19–21] However, MALDI-TOF MS is not infallible. The absence of identification or misidentification of fungal species by MALDI-TOF MS is essentially attributable to the absence, inaccuracy, or incompleteness of reference spectra in the database.[9,21] This limitation is particularly consequential for rare or cryptic NAC species. For instance, *C. viswanathii* is consistently misidentified as *C. tropicalis* by MALDI-TOF MS, with low discrimination scores of 1.6–1.7 reported regardless of the preparation method employed, highlighting the current limitations of commercial MALDI-TOF MS libraries for rare species.[22]

Molecular methods, including internal transcribed spacer (ITS) sequencing and PCR-based approaches, are considered the gold standard for resolving discordant identifications between phenotypic and MALDI-TOF MS results.[23–25] However, these methods are costly, time-consuming, and not readily available for routine identification at most clinical sites.[26]

According to the data above, identification of uncommon Candida species remains challenging, and discordant results may occur between phenotypic, proteomic, and molecular methods, potentially affecting definitive species determination. Therefore, this study aims to describe a rare case of non-albicans Candida bloodstream infection in an immunocompromised patient, with emphasis on the diagnostic challenges and clinical implications of discordant laboratory identification in guiding appropriate management.

CASE DESCRIPTION

A 48-year-old female entered the emergency room with complaints of bleeding from the vagina for two months. The patient also reported reduced urine output for two days before admission, as well as nausea and vomiting occurring 3–4 times a day. There was a weight loss over two months, from 53 to 47 kg.

Patient diagnosed with chronic kidney disease and underwent placement of a double-lumen catheter (DLC) in the right thigh for hemodialysis access. The patient has a history of hypertension and is treated with telmisartan 8 mg. The patient was diagnosed with cervical cancer and chemotherapy.

The result of histological analysis of cervical tissue in the form of non-keratinising squamous cell carcinoma. Ultrasound of the whole abdomen found a mass in the lower segment of the uterus, which had infiltrated the posterior wall of the left side of the urinary bladder and spilt into the proximal 1/3 of the vagina.

The medical devices used for the patient were intravenous catheters, parenteral nutrition, DLC, CVC, and urine catheters. On the 14th day of admission, the patient lost consciousness (GCS 9 E3M4V2) and was transferred to the ICU. Blood culture was performed on the 15th day of treatment, and the results were positive on the second day of incubation. The patient has increased levels of urea, 158 mg/dl, and creatinine, 13.6 mg/dl. Initial laboratory findings were remarkable for a white blood cell count of 30.990/dL, with polymorphonuclear leukocytes of 84.3%, Hb 10 g/dL, and platelets 533 $x10^3$/uL (150-450$x10^3$/uL. Ceftazidime (1.0 gr) was administered twice daily. A combination therapy of ceftazidime, moxifloxacin, and metronidazole for a patient in the ICU. Urinalysis revealed cloudy yellow urine, blood +++ (250 RBC/uL), +1 protein (30 mg/dl), and leukocytes ++ (750 WBC/uL). After 21 days of treatment, the patient died before receiving antifungal therapy.

During hospitalisation, the patient exhibited progressive clinical deterioration characterised by worsening general condition requiring intensive care unit (ICU) admission. She had multiple predisposing risk factors for invasive infection, including advanced cervical malignancy undergoing chemotherapy, end-stage renal disease requiring hemodialysis, and the presence of multiple indwelling medical devices, including central venous and dialysis catheters. Despite broad-spectrum antibiotic therapy and supportive care, the patient's condition continued to decline. Blood culture was obtained on day 15 of hospitalisation due to persistent clinical suspicion of sepsis.

Microbiology Laboratory tests

Culture on agar media

Blood culture was positive on the second day of incubation, and Gram staining was performed to obtain yeast appearance (**Figure 1**), then inoculated into SDA and stored in the incubator in ambient air at 37°C for 24 hours. *Candida* species was isolated and produced a small-sized, yellowish-white colour on SDA (**Figure 2**).

Identification and Antifungal Sensitivity Test (AST)

The VITEK® 2 YST system (bioMérieux) successfully identified *C. lipolytica* from blood cultures with a 91% probability. This isolate was sensitive to voriconazole, amphotericin B and flucytosine. Following initial identification using the VITEK® 2 YST system, further confirmation was performed using MALDI-TOF mass spectrometry to improve species-level accuracy, particularly in the identification of uncommon non-albicans Candida species that may be misidentified by conventional biochemical methods. *C. glabrata* (99.9%) was identified using Matrix-Assisted Laser Desorption Ionisation Time-of-Flight (MALDI-TOF) technology. Due to discordant results between VITEK® 2 and MALDI-TOF, molecular confirmation using PCR amplification of the ITS region followed by phylogenetic analysis was performed for definitive species identification.

DNA extraction and PCR amplification

The gSYNC™ DNA Extraction Kit (Gene aid®, Taiwan) was used for genomic DNA extraction and purification based on the guidelines. The PCR mixture was divided into 25 µL of GoTaq Master Mix, 6 µL of primer mix (which contained 1 µl of forward and reverse primers for each one), 9 µL of water, and 10 µL of DNA template for a total volume of 50 µL. The Bio-Rad thermal cycler was used to perform the PCR amplification. The PCR cycle parameters included an initial denaturation step at 95°C for 2 min, followed by 25 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 60 s. The final extension step was performed at 72°C for 10 min. Following amplification, 5 µL of PCR product was electrophoresed

at 100 V for 30 min to examine the PCR products using agarose gel electrophoresis on 2% agarose gels containing ethidium bromide. Following amplification, PCR products were confirmed by agarose gel electrophoresis and subsequently used for sequencing-based species identification.

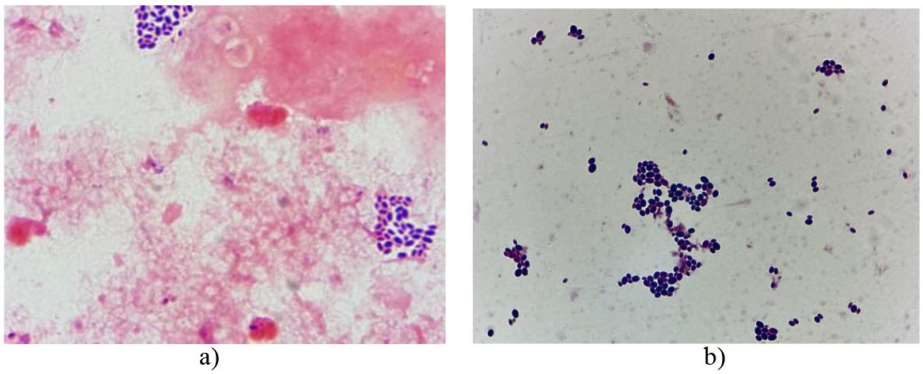
Phylogenetic analysis of *Candida* based on ITS gene sequencing

Understanding the evolutionary links and genetic similarities between various *Candida species* requires the use of phylogenetic analysis. DNA from the genome was isolated from the isolate, and the internal transcribed spacer (ITS) gene was amplified using specific primers (Figure 3).

DISCUSSION

Candida-related bloodstream infections are uncommon and challenging to diagnose. The factors that affect the prevalence of *Candida* include the species of *Candida*, patient populations, the availability of medical care facilities and training programs, infection control programs in hospitals, and techniques of surveillance.[27] Identification of *Candida* using conventional methods can result in the misidentification of uncommon *Candida* species. Uncommon *Candida* species initially reported by conventional methods, molecular methods may be used as an alternative, but may fail to identify some uncommon *Candida* species; confirmation by sequencing analysis is required.[28,29]

According to the history of these cases, *C. lipolytica* can be a causative agent in patients with intravascular catheter infection.[30] Based on culture, *C. lipolytica* was misidentified as *C. glabrata* if yeast cells were low or less than 10^6 CFU/ml, resulting in an incorrect identification. MALDI-TOF examination results found *C. glabrata,* and sequencing found similarity between isolates with *C. glabrata*. Conventional methods for identifying *Candida* may lead to incorrect identification of uncommon species. Although molecular-based methods can be used as an alternative to identify some uncommon *Candida* species that were identified by conventional methods, confirmation by sequencing analysis is



a) b)

Figure 1. Gram stain showed Yeast features: a) from blood culture, b) from colonies in Sabouraud Dextrose Agar (SDA). (*personal documentation*)

Figure 2. *Candida lipolytica* colonies on SDA. (*personal documentation*)

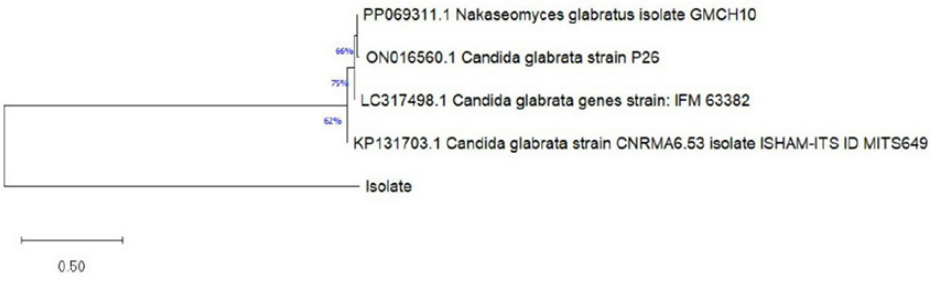


Figure 3. Phylogenetic tree based on sequencing of the ITS gene from the isolate.

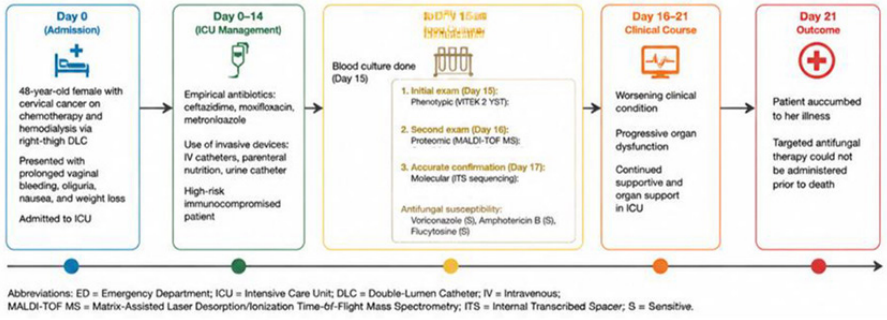


Figure 4. Case timeline flow chart

necessary. Pyrosequencing using different targets, such as ITS1, has been used to identify *Candida* pathogens in a variety of clinical samples, including blood samples, with results similar to conventional methods.[28]

In cases of candidemia, patients with severe disease have a significant mortality rate.[12] The factors that affect the prevalence of *Candida* include the species of *Candida*, patient populations, the availability of medical facilities and training programs, hospital infection control programs, and surveillance methods.[31] Clinicians should be aware that opportunistic pathogens such *as C. lipolytica* may cause invasive infections. A common problem is the lack of specific clinical findings suggesting a candidemia diagnosis for empiric antifungal therapy. Identify patients who are at risk of benefiting from empiric treatment for fungal bloodstream infections in appropriate clinical settings.[32]

The management of *C. lipolytica* candidemia is to provide adequate antifungal therapy and catheter removal.[30,33–36] Uncommon *Candida* isolates are more frequently associated with treatment failure due to azole resistance, which results in a poorer response and a longer duration of infection.[37] Treatment with voriconazole, caspofungin, micafungin, anidulafungin, and amphotericin B may be better and more effective than fluconazole or 5-fluorocytosine.[16,34,38] Patients with severe illness have a high mortality in cases of candidemia.[12]

The strengths of this case include the comprehensive stepwise microbiological investigation involving phenotypic, proteomic, and molecular methods, which allowed detailed evaluation of diagnostic discordance in identifying non-albicans Candida species. In addition, the case highlights a high-risk immunocompromised patient with multiple predisposing factors for candidemia, reflecting real-world clinical complexity. The presence of diagnostic uncertainty and delayed antifungal initiation further emphasises important clinical implications regarding early recognition and management of invasive Candida infections.

This case report has several limitations. First, as a single case, the findings cannot be generalised to a broader population. Second, the absence of a control group limits causal inference, particularly regarding the relationship between delayed antifungal therapy and clinical outcome. Third, the lack of repeated blood cultures and catheter tip cultures limited definitive identification of the infection source. Therefore, future studies should include a larger case series or multicenter cohort to better characterise the clinical spectrum, risk factors, and outcomes of rare non-albicans Candida bloodstream infections. In addition, prospective studies evaluating early empiric antifungal therapy and standardised catheter management protocols are needed to better define optimal treatment strategies and improve patient outcomes in high-risk immunocompromised populations.

CONCLUSION

Bloodstream infections caused by Candida species present significant diagnostic challenges, particularly in terms of rapid detection required for timely therapeutic intervention. This case highlights a rare non-albicans Candida bloodstream infection in an immunocompromised patient, emphasising the challenges in accurately identifying specific non-albicans Candida species. Therefore, a stepwise diagnostic approach involving sequential use of culture-based identification, proteomic analysis, and molecular confirmation is essential, as demonstrated in this case. The use of confirmatory molecular techniques such as PCR and phylogenetic analysis is crucial to ensure accurate species identification and to guide appropriate clinical management. Early recognition, comprehensive diagnostic evaluation, prompt antifungal therapy, and effective source control remain essential to improve outcomes in high-risk patients.

DISCLOSURE

Conflict Of Interest

The authors declare that they have no conflict of interest.

Author Contribution

VH, BM, ARS, MH, N, and FH were involved in concepting, designing, and supervising the manuscript. YDP and ULW conduct the study. All authors prepare the manuscript and agree to this final version of the manuscript being submitted to this journal.

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Ethical statement

Written informed consent for publication of this case report and any accompanying clinical data was obtained from the patient's legal representative.

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