GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(CASE REPORT)

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Mixed candidemia caused by *Candida tropicalis* and *Candida krusei*: A case report

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GSC Biological and Pharmaceutical Sciences, 2026, 34(01), 232-236

Publication history: Received on 18 December 2025; revised on 27 January 2026; accepted on 29 January 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.34.1.0032

Abstract

Mixed fungemia, defined as the isolation of two or more fungal species from the same sample, is rare and often underdiagnosed. It represents a diagnostic and therapeutic challenge due to its high morbidity and mortality. We report the case of a 66-year-old patient with type 2 diabetes mellitus and hypertension, hospitalized for obstructive pyelonephritis complicated by hyperosmolar coma. The clinical course was marked by mixed candidemia due to *Candida tropicalis* and *Candida krusei*, identified only after 10 days of blood culture incubation. The antifungal susceptibility test revealed variable sensitivity to antifungal agents, with the natural resistance of *C. krusei* to fluconazole. Despite appropriate antifungal therapy, the patient died following septic shock. This case highlights the rarity and severity of mixed fungemia, as well as the importance of early and accurate diagnosis to optimize management and improve prognosis.

Keywords: Fungemia; Mixed Candidemia; *Candida Tropicalis*; *Candida Krusei*; Mycological Diagnosis

1. Introduction

Fungal bloodstream infection is a serious opportunistic nosocomial infection associated with a high mortality rate [4,5]. It is the most common form of invasive fungal infection and is mainly caused by species of the genus *Candida*, rarely by *Malassezia, Geotrichum, Trichosporon, Rhodotorula,* or *Saccharomyces* [1,2,6–9]. The increase in species that are resistant or have reduced sensitivity to conventional antifungal agents is a cause for concern [4,10].

The majority of fungemia cases are considered to be monomicrobial [11,12], while mixed fungemia, defined as the isolation of two or more fungal species, remains rare and poorly documented [13–16]. Their management is complex, as accurate identification of all causative agents is essential for appropriate treatment. With the increase in the number of immunocompromised patients and improvements in diagnostic methods, the likelihood of encountering mixed fungemia, particularly mixed candidemia, is on the rise [12,17].

We report here a rare case of mixed candidemia to highlight the associated diagnostic and therapeutic difficulties.

2. Observation

This is a 66-year-old patient, a chronic smoker, with a history of type 2 diabetes treated with insulin and high blood pressure treated with antihypertensive medication.

The patient initially consulted for pain in the left iliac fossa accompanied by signs of lower urinary tract involvement: dysuria, urinary incontinence, and burning during urination. The course was marked by febrile left low back pain with, on clinical examination, bilateral lumbar tenderness, hypogastric tenderness, and pyuria.

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Urinalysis was positive for *Klebsiella pneumoniae*. A CT urogram revealed a non-obstructive microcalculus in the lower calyx of the right kidney and moderate dilatation of the pyelocaliceal cavities and subpyelical ureter of the left kidney upstream of a macrocalculus lodged in the ureteral meatus.

The patient subsequently developed complications including acute obstructive renal failure with anuria, hypernatremia, hyperglycemia, and thrombocytopenia, leading to hyperosmolar coma. Medical treatment was administered, including beta-blockers, anticoagulants, antibiotics (amoxicillin/clavulanic acid then C3G, then a combination of vancomycin and imipenem) and antifungals (fluconazole), combined with several hemodialysis sessions. He also underwent transfusions of packed red blood cells and platelets during dialysis. Surgery involving insertion of a left JJ stent was performed for obstructive pyelonephritis.

Given the persistence of urinary symptoms, a mycological examination of the urine was requested, along with a fungal blood culture. The mycological examination, performed on Sabouraud chloramphenicol medium with semi-quantitative seeding followed by incubation at 37°C, showed a monomicrobial culture on the second day, revealing significant candiduria (10^6 CFU/mL). Identification, performed using the VITEK 2 automated system (BioMérieux), revealed *Candida tropicalis*. The antifungal susceptibility test showed that the strain was sensitive to all antifungal agents tested.

The fungal blood culture bottle, incubated in the BACTEC automated system, became positive after 10 days. Identification of the colonies revealed two species of yeast: *Candida tropicalis* and *Candida krusei*. The antifungal susceptibility test showed that *Candida tropicalis* was multi-sensitive, while *Candida krusei* was resistant to fluconazole (natural resistance) and 5-fluorocytosine.

The clinical course was marked by worsening consciousness disorders, which were aggravated by septic shock of urinary origin due to a left ureteral stone. Despite treatment, the patient died.

3. Discussion

In recent years, the frequency of invasive fungal infections has increased significantly among hospitalized patients worldwide [1-3]. Mixed fungemia is rare compared to fungemia as a whole: according to several studies, its incidence varies from 2 to 10% [11–16]. In our study, out of 69 positive blood cultures, only 2 were positive for two fungal species, or 0.08%.

However, according to some authors, this incidence is underestimated, particularly when blood cultures are inoculated onto standard media such as Sabouraud medium, on which species of the genus *Candida* are difficult to distinguish.

The diagnosis of mixed fungemia was confirmed by blood cultures, and detection was facilitated by transferring the initial cultures to chromogenic media or by certain PCR variants that can detect fungal DNA and identify the species involved [26–29]. Fungal bottles are potentially more effective at detecting fungemia than aerobic bottles [30–32]. Bacterial co-infection can also complicate the isolation of fungi in blood cultures. The type of medium used for subculturing from yeast-positive bottles also influences the detection of mixed fungemia. Most yeasts produce similar colonies on Sabouraud agar, which complicates their reliable differentiation.

Klotz et al. showed that, among blood cultures isolating *Candida*, 23% were polymicrobial, combining *Candida* and other organisms, and 4% were positive for more than one *Candida* species [16]. According to data in the literature, *C. albicans* is present in the majority of cases of mixed fungemia. The most common combination is *C. albicans*–*C. glabrata*, followed by *C. albicans*–*C. tropicalis*, then *C. albicans*–*C. parapsilosis* [12-14,16]. These frequencies can be explained by the frequencies of the main species encountered in human pathology, particularly in candidemia.

A Malaysian study also showed that the incidence of mixed candidemia is relatively low, ranging from 2 to 9.3% of all candidemia cases [4,15]. *Candida albicans* is the species most often involved in mixed candidemia in this study, which is consistent with other studies. The most common combinations were *C. albicans* + *C. glabrata* [17] and *C. albicans* + *C. parapsilosis* [12]. Other species such as *C. tropicalis*, *C. krusei*, *C. dubliniensis*, and *C. glabrata* have also been reported as causes of mixed candidemia [12,17]. These results are consistent with our observation, in which mixed candidemia involved *Candida tropicalis* and *Candida krusei*.

Mixed fungal infections develop particularly in immunocompromised patients. Neutropenia, prolonged hospital stays, the use of broad-spectrum antibiotics, exclusive parenteral nutrition, and the presence of central venous catheters have been demonstrated in several studies to be risk factors [4,24]. The main risk factor is the presence of vascular access with a prolonged stay in intensive care. All these factors are well known to predispose patients to fungemia, particularly

candidemia [1,8,19,20]. In our patient, the predisposing factors were a prolonged stay in intensive care and the presence of vascular access.

Mixed fungemia does not appear to differ from monomicrobial fungemia in terms of predisposing factors, clinical presentation, treatment modalities, and the efficacy of antifungal treatments, which is consistent with the majority of data reported by several authors [6,11–14,18]. However, some authors believe that antifungal monotherapy is insufficient for optimal management and is associated with a higher mortality rate in patients with mixed fungemia [13]. Our patient received fluconazole monotherapy antifungal treatment, but the delay in diagnosis led to a delay in the administration of the antifungal agent, resulting in the patient's deterioration and eventual death.

Yapar et al. showed that the main finding of their study was the higher mortality observed in patients with mixed candidemia, and that this leads to a poorer prognosis, possibly due to a higher yeast load [25]. The contribution of antifungal combinations in the treatment of mixed fungemia remains to be evaluated in large series, which is relatively difficult given the rarity of these infections. However, therapeutic adaptation in mixed fungemia, according to the species identified and their sensitivity profile to antifungals, remains essential for a better therapeutic response.

4. Conclusion

Mixed fungemia is rarely diagnosed and accounts for approximately 2% of fungemia cases. It appears to be similar to monomicrobial fungemia in terms of risk factors, clinical presentation, and prognosis.

Given that the clinical characteristics associated with the onset of mixed candidemia are not well defined, and considering the small number of patients with this condition in this study, further studies are needed, including in vitro systems or animal models, as well as large-scale multicenter clinical data.

Mixed candidemia is a significant predictor of mortality. Due to the limitations of conventional microbiological techniques, it was generally considered to be an infection caused by a single *Candida* species, leading to underdiagnosis and therefore delays in appropriate management.

Given the poor prognosis associated with this condition, other known risk factors for mortality, such as inappropriate antifungal treatment or delayed catheter removal, should be rigorously controlled in these patients in order to improve their often poor prognosis.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

Statement of informed consent

Informed consent was obtained by all participants in this study.

Funding information

The author(s) received no specific grant from any funding agency.

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