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Case presentation

Folliculocentric cutaneous presentation of disseminated *Candida krusei* infection in a patient with acute myeloid leukemia

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Abstract

Candida krusei (*C. krusei*) is a multidrug-resistant opportunistic fungal pathogen that may cause disseminated infections in immunocompromised hosts. However, its clinical and histologic features are not well-characterized. We present a unique case to contribute to the growing knowledge base associated with this organism. During hospitalization for neutropenic fever, a 19-year-old man with acute myeloid leukemia, who underwent hematopoietic stem cell transplantation, developed a generalized folliculocentric eruption following initiation of antifungal therapy for newly diagnosed *C. krusei* fungemia. Despite adequate antifungal coverage and negative blood cultures, the follicular-based erythematous papules persisted. Biopsies demonstrated yeast within ruptured follicles, without angiotropism or involvement of the interfollicular dermis, subcutaneous tissue, or stratum corneum. Concurrent skin tissue cultures confirmed *C. krusei*. The patient remained febrile despite aggressive antifungal therapy, with relapse of leukemia and subsequent death. Our case is unusual given the development of cutaneous lesions following clearance of fungemia, with yeast limited to ruptured follicular lumina, possibly indicating a primary cutaneous source or early transfollicular/transepidermal elimination. Given the limited available descriptions of cutaneous histopathology for C. krusei, we seek to add to the understanding of its pathophysiology and aid in the diagnosis and treatment of this often fatal infection.

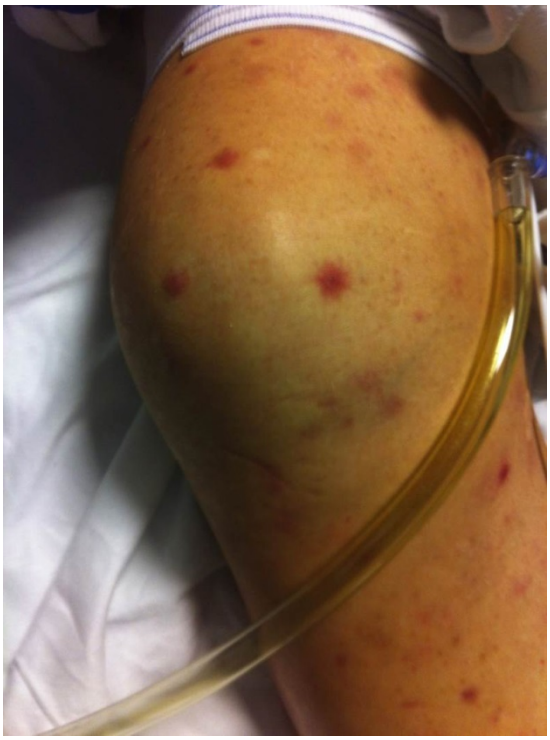
Keywords: fungemia, candida krusei, immunocompromised host

Introduction

C. krusei is a fungal organism, which has emerged in recent decades as an important pathogen in nosocomial infections. Widely found in nature, *C. krusei* was originally considered to be a sporadic isolate in humans without much clinical significance. However, a growing body of literature implicates the organism as a causative agent in human disease, most importantly in disseminated fungemia among immunocompromised patients. Systemic infection is associated with a high mortality rate, such that early recognition of cutaneous manifestations may prove valuable in management [1, 2]. However, relevant clinical literature on this organism remains sparse. We present a case of disseminated *C. krusei* infection in an immunocompromised patient with unusual clinical and histopathologic attributes.

Case synopsis

A 19-year-old man with acute myeloid leukemia status post hematopoietic stem cell transplantation was hospitalized for persistent pancytopenia and neutropenic fever, and was diagnosed with *C. krusei* fungemia. Extensive testing for source, including multiple computerized tomography scans and transthoracic echocardiogram, were negative for gastrointestinal, pulmonary, and cardiac valve sources of infection. His central line was removed early during the admission, with a negative tip culture. Ultrasound of the limbs revealed only focal areas of swelling on the arms. He was subsequently started on intravenous micafungin and voriconazole for persistent fungemia. Several days after initiation of antifungals, despite negative blood cultures, he developed an erythematous rash on the scalp and bilateral upper and lower extremities. His vital signs were pertinent for fever (38.8 C), hypotension (101/55 mm Hg), tachycardia (122/min), and tachypnea (22/min). On physical exam, he had a white plaque on the tongue consistent with thrush. On the left proximal arm, he had a warm, indurated, erythematous plaque. He also had follicular-based erythematous papules on the scalp and bilateral upper and lower extremities (Figure 1). There were erythematous papules on the left palm and right plantar surface. The papules were slightly pruritic and tender to palpation. His laboratory studies were significant for hemoglobin of 9 g/dl and hematocrit of 26%, white blood cell count of less than 50/µL, and platelet count of 37,000/µL. His fungal blood cultures remained negative. The differential diagnosis based on clinical findings included disseminated candidiasis, other disseminated fungal or bacterial infection, infectious folliculitis, and leukemia cutis.



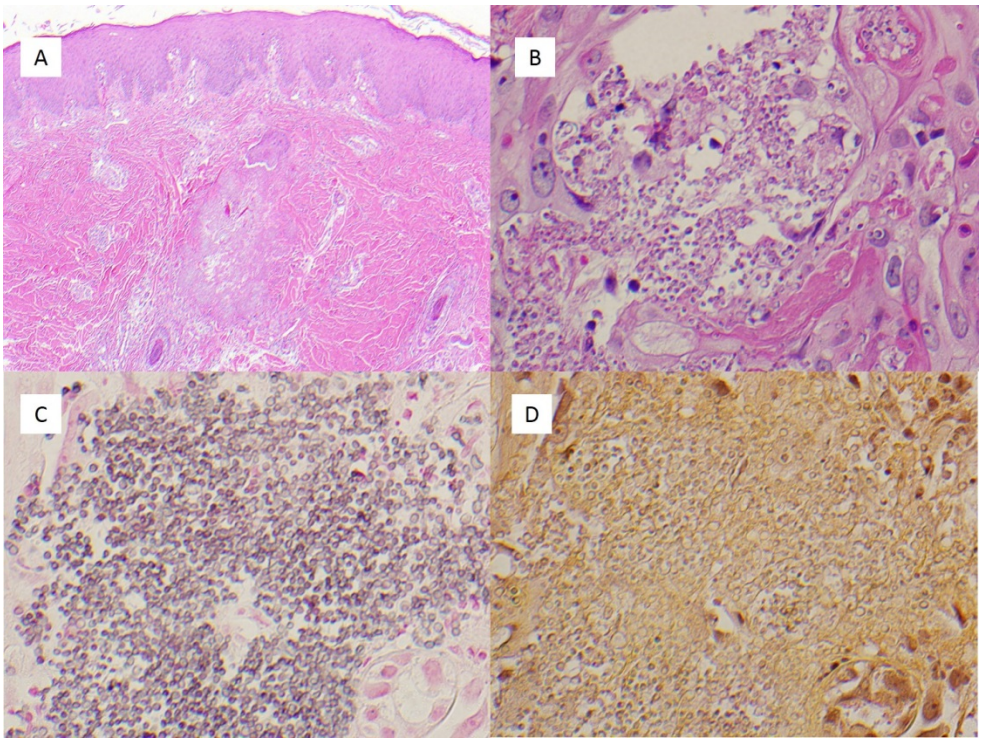


Figure 1. Clinical morphology. On clinical examination, the patient demonstrated follicular-based erythematous papules on the scalp and upper and lower extremities. **Figure 2.** Yeast morphology and staining characteristics. A, on histologic examination, sheets of budding yeast are limited to the vicinity of an obliterated hair follicle. The epidermis, adjacent dermis, and subcutis are uninvolved, and there is a virtual absence of inflammation (right arm, hematoxylin-eosin [H&E], original magnification x200). B, yeast diameters measure 3-5 microns (left arm, H&E, original magnification x600). C, Fontana-Masson was weakly positive, not previously described in C. krusei (left arm, Fontana-Masson, original magnification x600). D, Mucicarmine was negative for a mucoid capsule, as classically seen in Cryptococcus neoformans (left arm, mucicarmine, original magnification x600).

Two 4-mm punch biopsy specimens were obtained from separate papules on the right arm and left arm. On histologic examination, both biopsies revealed sheets of budding yeast, limited to the vicinity of obliterated hair follicles. The epidermis, adjacent dermis, subcutis, and blood vessels were uninvolved, demonstrating a virtual absence of inflammation (Figure 2A). The yeast forms measured 3-5 microns in diameter, with slight size variability (Figure 2B). There was evidence of edema and an increased number of histiocytes surrounding follicles. Periodic acid-Schiff and Grocott methenamine silver stains of the second biopsy (left arm) highlighted the organisms, as did a Fontana-Masson stain (Figure 2C). A mucicarmine stain, which highlights the mucoid capsule of most *Cryptococcus* species, was negative (Figure 2D). These histopathologic findings suggested a differential diagnosis of *C. krusei* (primary versus hematogenous), *Pityrosporum/Malassezia* species (primary), and capsule-deficient *Cryptococcus neoformans* (primary versus hematogenous).

Concurrent tissue cultures from the biopsy specimens later confirmed *C. krusei*. The patient remained febrile despite appropriate combination intravenous antifungal therapy. Unfortunately, the patient's leukemia relapsed, and he expired shortly thereafter.

Discussion

In recent years, there has been a rising incidence of disseminated candidiasis (DC), especially in hospitalized immunocompromised patients [1]. DC is associated with a high mortality rate, ranging from 46 to 75%, often related to a delay in diagnosis given the nonspecific clinical presentation and lack of more rapid diagnostic tools. Several risk factors for the development of DC have been highlighted in the literature. These include hematolymphoid malignancy, intensive cytotoxic chemotherapy, ablative radiation therapy, and prolonged use of broad-spectrum antibiotics [3]. The most common causal organism in DC is *Candida albicans*, whereas the most common organism found in cutaneous lesions in DC is *Candida tropicalis* [1].

C. krusei is less prevalent and has been considered less virulent than these species. The earliest reports of systemic *C. krusei* infections were documented in the 1960s. However, there is growing evidence that multidrug resistant *C. krusei* incidence is rising among patients who receive prophylactic fluconazole. The gastrointestinal tract is the most frequently colonized location, followed by the upper respiratory and genitourinary tracts [2]. Isolates of *C. krusei* from non-sterile sites often represent colonization rather than infection. However, colonization with *C. krusei* has been reported to precede infection in approximately 70% of patients, with possible therapeutic significance [4]. Disseminated *C. krusei* infection has also been shown to exhibit higher mortality rates than disseminated *C. albicans* infections [5].

The most common initial clinical symptom of DC is fever recalcitrant to multiple antibiotics, with cutaneous lesions as the most common initial sign, seen in 13 to 36% of patients [1, 6]. The presence of cutaneous findings is associated with a history of hematologic problems such as leukemia and aplastic anemia. These lesions usually begin as macules and then become papular, pustular, or nodular, frequently with an erythematous halo and a pale central clearing. Occasional necrosis and crusting of the lesions may be observed [1, 3]. Many patients develop a generalized rash, whereas others demonstrate skin manifestations localized to lower extremities, or lower extremities and palms. Nodular folliculitis and plaques on the bilateral shins resembling cellulitis have also been reported [1, 3]. Among heroin users, a distinct syndrome of cutaneous, ocular, and costochondral manifestations has been described [7]. As for clinical findings specifically observed in disseminated *C. krusei*, few accounts are available in the literature and are generally considered similar to DC presentations caused by other species. Hager and colleagues' report of *C. krusei* fungemia in an immunocompromised patient described the cutaneous findings as a generalized eruption of erythematous papules, with necrosis and some crusting [5]. Pedraz and colleagues reported a rapid eruption of erythematous, well-defined papules, some of which had a central pustule [3].

Histology plays an important role in the diagnosis of DC, since the clinical features can vary and be nonspecific. Furthermore, in approximately 50-75% of cases, blood cultures may be negative [8]. The histopathologic features associated with DC caused by the more common *Candida* species (*C. albicans* and *C. tropicalis*) typically show small aggregates of fungal organisms in the dermis, around and within blood vessels. These aggregates typically localize to sites of vascular damage that may include thrombotic or vasculitic injury, likely caused by trapped *Candida* organisms during hematogenous dissemination [1, 3]. A single instance suggestive of transepidermal elimination has been reported in the literature, in which fungal organisms were found in the upper dermis, stratum corneum, and stratum spinosum. The epidermis has otherwise been reported to be intact in cases of DC, except for a few cases in which vesicles were present in the epidermis, without organisms, and these may have represented concurrent herpesvirus infection [1]. Overall, the histopathologic manifestation of DC differs from that of chronic cutaneous candidiasis, in which fungal organisms are observed within the stratum corneum [6]. The observation of *Candida* organisms is commonly limited to only some sections of the specimens, such that special stains and multiple levels may be important for detection in suspected DC [1]. With DC related to *C. krusei*, one report described biopsy findings of aggregates of yeast forms within the superficial dermis [5], and another described intravascular thrombi and perivascular yeast forms, similar to the features characteristic of DC caused by other species [3]. However, descriptions of *C. krusei* cutaneous histopathology are currently sparse.

Although this patient's presentation, including the morphology of his skin lesions, was consistent with previous reports, his case was unusual given the development of follicular-based erythematous papules following treatment and clearance of fungemia. Interestingly, this patient's biopsies demonstrated yeast limited to the vicinity of ruptured follicular lumina, which is not characteristic of hematogenous dissemination. No fungal organisms were detected within the overlying stratum corneum or surrounding dermal or subcutaneous tissues. These biopsy features may indicate a primary cutaneous source or possible early transfollicular/transepidermal elimination. Another noteworthy finding is the positive staining for Fontana-Masson. This stain detects melanin and can be employed to identify dematiaceous fungi. Positive staining may be seen in *Cryptococcus* or *Pityrosporum*, and has not been previously reported in *C. krusei* [9,10]. Capsule-deficient *Cryptococcus neoformans* infection, which is seen more commonly in immunocompromised patients, may show a similar staining pattern to this case (positive for Fontana-Masson and negative for mucicarmine), but the yeast diameter of 3-5 μm observed in this patient's specimens are small for *Cryptococcus* (typically 5-10 μm) [11]. *Candida albicans* yeast are 3-6 μm in diameter [12], whereas *Pityrosporum (Malassezia)* yeast are 2-5 μm in diameter [13]. Review of the literature shows that the more common *Candida* species (*C. albicans* and *C. tropicalis*) have consistently demonstrated negative staining with Fontana-Masson, whereas *C. krusei* has not been included in prior investigations [9]. Other authors have pointed out significant differences in structure, metabolism, and response to host defense between *C. krusei* and the more common *Candida* species, even arguing for taxonomical recategorization [2]. The

details in this case help to highlight some aspects of *C. krusei* which may distinguish this organism from other species that cause DC.

Upon diagnosis, treatment must be initiated immediately given the high mortality rates. Fluconazole is first-line for systemic *C. albicans* infections, whereas less data are available regarding treatment options for the other *Candida* species [3]. Insufficient efficacy of fluconazole as treatment and as prophylaxis against *C. krusei* has been documented [2]. There has also been increased resistance against flucytosine reported in recent years. Empiric treatment with amphotericin B, voriconazole, or an echinocandin is the typical course of action until susceptibility data are available [5]. However, decreased susceptibility of *C. krusei* to these antifungal agents has been discussed in the literature [4, 14, 15]. Awareness of such trends may help to reduce morbidity and mortality from this infection.

Conclusions

This patient's case sheds light on the clinical and histopathologic characteristics of disseminated *C. krusei* infection, which may help to distinguish this organism from other causative agents of DC. This case is unusual given the development of cutaneous lesions following treatment and clearance of fungemia, with two biopsies from separate sites demonstrating yeast limited to the vicinity of ruptured follicular lumina, which is not characteristic for hematogenous dissemination. These findings may indicate a primary cutaneous source or possible early transfollicular/transepidermal elimination. We seek to add to our understanding of this pathogen and increase awareness among clinicians regarding this potentially fatal infection.

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