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Letter to the Editor

A Case of Central Venous Catheter-Related *Candida parapsilosis* Fungemia Evolved to Disseminated Infection in a Neutropenic Patient with Blast Crisis of Chronic Myeloid Leukemia

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To the editor.

We want to comment on a case of invasive, potentially lethal *Candida parapsilosis* disseminated infection in a neutropenic patient affected by chronic myeloid leukemia with blast crisis to underline the importance of removing the central venous catheter (CVC) as a potential source of infection as soon as possible during candidemia, without replacing it with other polyurethan intravascular devices.

C. *parapsilosis* fungemia associated with intravascular device infections is reported in onco-hematological patients,[1] in which central venous catheters are largely used, representing reliable intravascular access essential for chemotherapy administration and intensive supportive care. Several distinct features that help the spread of *C. parapsilosis* are the ability to develop biofilms on intravascular devices and the high affinity for parenteral nutrition.[2]

Catheter removal together with antifungal treatment is almost always required for resolution of *C. parapsilosis* catheter-related fungemia; however, the immediate removal of the infected device may be difficult in these high-risk patients, especially in severe clinical conditions such as persistent febrile neutropenia, leading to a prolonged fungemia and invasive infection.

Here we report a case of a 47 years-old man affected by a relapsed blast crisis of chronic myeloid leukemia, hospitalized in June 2022 to receive reinduction chemotherapy with Fludarabine plus Idarubicine and High-dose Cytarabine together with the tyrosine-kinase inhibitor (TKI) Ponatinib. The patient had been carrying a peripherally inserted central venous catheter (PICC) for one year. Total Parenteral Nutrition (TPN) was started six days after chemotherapy initiation; Posaconazole antifungal prophylaxis was not administered because of drug-drug interaction between Posaconazole and TKI.[3] On day seven from chemotherapy start, the patient developed febrile neutropenia (neutrophil count: 190/mL), and empiric antibiotic therapy with Piperacillin/Tazobactam (4.5 g every 8h) and Tigecycline (100 mg loading dose, then 50 mg q 12h) was initiated and the day after, three blood cultures drawn from PICC at the onset of fever, resulted positive for *C. parapsilosis*. Drug-drug interactions with Ponatinib hampered the use of triazoles, and, according to IDSA guidelines,[3] systemic antifungal therapy with Caspofungin (70 mg loading dose, then 50 mg daily) was started. No gastrointestinal colonization with *C. parapsilosis* was found, and chest and maxillo-facial CT scans without contrast resulted in negative for suspected fungal localizations. Two days after the start of antifungal therapy, the *in vitro* antifungal sensitivity test showed good activity of Caspofungin against the *C. parapsilosis* isolate; however, fever persisted, and Piperacillin/Tazobactam was empirically substituted with Meropenem (1 g q 8h).

Five days after the first positive blood samples, the patient persisted highly febrile and hemodynamically unstable, and all blood cultures persisted positive for *C. parapsilosis*. The PICC was removed, and a peripheral polyurethane vascular catheter was inserted. The PICC tip culture was negative, and the transthoracic echocardiogram and total body CT scan without contrast were both negative. Six days after starting Caspofungin therapy and four days after PICC removal, all blood cultures persisted positive for *C. parapsilosis*. The patient's clinical conditions worsened, and he developed multiple nodular-papule purple skin lesions with a 1 - 5 mm diameter, localized on the legs, forearms, and hands. The needle aspiration of one lesion, performed for microbiological examinations, showed *C. parapsilosis* positivity within 24 hours. On day 8, blood cultures persisted positive for *C. parapsilosis*. Hence, the peripheral polyurethane vascular catheter was removed and substituted with a metallic tip catheter, and TPN was stopped. On day 9, the patient was persistently

febrile, and blood cultures persisted positive for *C. parapsilosis*. Hence, Caspofungin was substituted with liposomal Amphotericin B (2.5 mg/Kg daily). The day after, the patient became afebrile, and three days later, we obtained the first negative blood culture, after 14 days of persistent *C. parapsilosis* fungemia. In the subsequent days, the patient started to recover from neutropenia with the improvement of clinical conditions. While still maintaining liposomal Amphotericin B treatment, the patient underwent an ocular fundus exam which showed bilateral periocular retinal exudates strongly suggestive of candida endophthalmitis. The patient was discharged in good clinical conditions 27 days after the start of febrile neutropenia and in morphologic remission of his hematological malignancy. A progressive improvement in ocular and skin lesions was observed. He continued antifungal therapy with liposomal Amphotericin B every other day on an outpatient basis for a total of 40 days of treatment until the new hospitalization for allogeneic stem cell transplantation.

Our patient presented several risk factors for PICC-related *C. parapsilosis* fungemia and invasive candidosis: an intravascular catheter, parenteral nutrition administration, immune deficiency due to the hematological malignancy (mostly described for acute leukemia),[4] chemotherapy-related profound neutropenia[5] and absence of antifungal prophylaxis.

The link between CVC and *C. parapsilosis* has been described by several authors. Catheter removal is an important therapeutic intervention for the resolution of *C. parapsilosis* fungemia, possibly overcoming the necessary antifungal therapy, which, alone, may be ineffective despite the susceptibility of the fungus to the drug itself,[6] as occurred in our patient. In a retrospective study on 323 episodes of candidemia in cancer patients, Sun M. et al. observed that hematological malignancy, neutropenia, parenteral nutrition, and receipt of chemotherapy were associated with *C. parapsilosis* candidemia and candidemia due to removal of CVC < 72h was associated with 30-day survival (OR 0.248; 95% CI 0.067 – 0.915).[7] In a retrospective analysis of candidemia in hematologic malignancy and/or stem cell transplant patients, Sipsas et al. found a high proportion (59%) of catheter-related candidemia episodes due to *C. parapsilosis* and other non-albicans Candida species.[5]

Puigh-Asensio et al., in a prospective, population-based surveillance study on oncological and hematological patients, found that catheters were the most frequent established source of candidemia and concluded that their removal is desirable especially in cases due to *C. parapsilosis* because of its association with intravascular device infections.[1]

Almost all the studies descriptive of disseminated candidiasis with skin and ocular involvement occurring in the setting of induction therapy for acute leukemia show that this was caused by Candida species known to be more aggressive than *C. parapsislosis*, such as *Candida tropicalis* (68%) and *Candida krusei* (15%).[4,8-10] The mortality rate of acute disseminated candidiasis with skin involvement, which occurred in the setting of neutropenia after induction therapy, was 45.4%.[4] The most commonly observed skin lesion pattern is erythematous or purpuric maculopapular lesions disseminated through the trunk and extremities.[4] McQuillen et al., reporting three cases of invasive infections characterized by endophthalmitis and skin lesions due to *C. krusei* in leukemia patients, observed that common risk factors for sustaining fungemia were prolonged intravenous catheterization and neutropenia.[10]

In a retrospective analysis of 35 *C. parapsilosis* cases of fungemia in patients with hematologic malignancies conducted at our institution,[6] the association between hospitalization and *C. parapsilosis* fungemia seemed largely due to the use of invasive medical devices and parenteral nutrition, strongly influencing the therapeutic approach and patients outcome. 94% of *C. parapsilosis* fungemia occurred in patients with CVC, receiving TPN in 54% of cases; *C. parapsilosis* invasive infection was observed in 3 patients (9%), fatal in all cases. CVC was removed in 23 patients: defervescence and fungemia clearance within 24 hours after catheter removal were observed in all but one (4%) who died persistently fungemic for a clinically suspected *C. parapsilosis* invasive infection. Ten patients maintained the CVC "in situ": the antifungal therapy without CVC removal was effective in obtaining the clearance of fungemia in 3 patients, while fungemia persisted in 7, all died, two of which for *C. parapsilosis* invasive infection.

In our patient, the delay in vascular catheter removal facilitated the spreading of a microorganism known to be not very virulent, but that revealed its ability to cause a potentially lethal disseminated infection in a deeply immunocompromised host. Central vascular access removal is often a difficult decision in high-risk patients. In our case, we delayed PICC removal because the patient was hemodynamically unstable during the fungemia. Once the PICC was removed, instead of a metallic tip catheter (inadequate to sustain the needed conduit of high volume of fluids, life-saving endovenous drugs, and TPN), we inserted a plastic tip peripheral vascular catheter, which probably became colonized by *C. parapsilosis* representing the source of the persistent fungemia even after PICC removal.

Two factors are probably related to the favorable outcome of our patient: firstly, the disseminated infection was due to a species of Candida, less pathogen than other species,[2,6] responding to antifungal therapy once removed the source of infection; secondly, blast crisis arising from chronic myeloproliferative disease might have produced less prolonged neutropenia compared to that of "de novo" acute leukemias.

Despite the impact of CVC removal on the outcome

of patients with candidemia, it is controversial. Studies reported discrepant results depending on the time of CVC removal;[11] in our experience, in the presence of *C. parapsilosis* fungemia in immunocompromised neutropenic patients, CVC and any other plastic catheters should be removed as soon as possible because of the known high-risk of their involvement in the fungemia. The infection's source persistence, leading to persistent fungemia despite the best antifungal therapy administered, represents a serious risk of disseminated, potentially lethal infection.

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