Dear Editor,

Resistance of Candida species to azoles has increased in recent decades, and echinocandin resistance has emerged as a new problem in some species [1]. The global prevalence of echinocandin resistance in Candida ranges from 0 to 2.8%, but is very rare in C. albicans; moreover, fluconazole resistance was detected in only 0.4% of C. albicans samples, but in 11.9% and 11.6% of C. glabrata and C. tropicalis samples, respectively [2]. The emergence of echinocandin resistance in species with a high frequency of azole resistance raises the specter of a multidrug-resistant fungal pathogen, which appears to be the case for C. glabrata [1]. In Korea, up to 2.6% of Candida species show fluconazole resistance, with particularly high frequencies in C. glabrata and C. krusei; however, fluconazole-resistant C. albicans is rare [3].

Here, we report a case of multidrug-resistant C. albicans (resistant to fluconazole and echinocandins) isolated from the bloodstream of a 27-yr-old male patient with B cell acute lymphoblastic leukemia (B-ALL) who received allogenic stem cell transplantation (SCT). He took micafungin as a prophylactic antifungal treatment for over three weeks, followed by oral fluconazole for intermittent oral candidiasis. Six months after SCT, he was hospitalized owing to relapsed B-ALL and received re-induction chemotherapy. While on fluconazole for neutropenic fever and oral candidiasis, the antifungal agent was switched to caspofungin on hospital day 20 owing to a prolonged neutropenic fever, and was then switched to amphotericin B on day 46 after another fever developed.

Peripherally drawn blood cultures were obtained on day 74 when the patient’s body temperature was 37.6°C. One of the two sets was positive for the growth of yeast, which was identified as C. albicans by the Vitek2 YST identification card system (bioMérieux, Marcy l’Etoile, France), representing the first C. albicans isolate from this patient.

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Antifungal susceptibility testing was performed by using the Vitek2 system and broth microdilution according to the CLSI guidelines [4]. The isolate was resistant to fluconazole, voriconazole, micafungin, and caspofungin (Table 1). For molecular confirmation of echinocandin resistance, the hot-spot regions of FKS1 were amplified and sequenced according to the previously outlined protocols [5]. The isolate had a homozygous T1933C mutation resulting in an S645P substitution, which was previously associated with micafungin treatment failure [5]. No specific mutation in ERG11, related to azole resistance, was detected.

Azole resistance can occur in C. albicans through diverse mechanisms such as overexpression of the multidrug transporter genes CDR1, CDR2, or MDR1, or by overexpression of ERG11, which encodes the azole target. The current patient received empirical caspofungin as of day 81 on the basis of the antifungal susceptibility test. Except for the initial isolation, follow-up blood cultures were all negative; however, the patient's general condition significantly worsened, and he died on day 88.

This is the first Korean case of echinocandin resistance in C. albicans, which was proven to have the FKS1 mutation. Echinocandins act by inhibiting β-1,3-D-glucan synthase, which synthesizes β-1,3-D-glucan of the fungal cell wall. Mutations of FKS genes (FKS1 and FKS2) encoding β-1,3-D-glucan synthase subunits lead to echinocandin resistance, and are detected in only 4% and <1% of C. glabrata and C. albicans isolates, respectively [6]. In Korea, Cho et al [7] reported an echinocandin-resistant C. glabrata isolate with an FKS mutation, but there has been no previous report of C. albicans with an FKS mutation.

Considering the extreme rarity of echinocandin resistance in C. albicans, our case suggests that immunocompromised patients, who are more likely to receive antifungal treatment as prophylaxis or for an invasive fungal infection, may have an increased risk of developing resistance. Recently, echinocandins have been used as first-line agents for the treatment of disseminated candidiasis and in antifungal prophylaxis [8, 9]. Echinocandins resistance can lead to treatment failure for candidiasis, resulting in prolonged treatment periods, increased complications, and even higher mortality [1, 6]. Although FKS mutations are uncommon among non-C. glabrata species, even with prior echinocandin exposure [6], clinicians should be aware of the potential for echinocandin resistance among patients with prior echinocandin exposure, especially those with breakthrough infections.

In conclusion, we report a case of breakthrough fungemia due to C. albicans with an FKS1 mutation in a patient with a hematologic malignancy. Clinicians should be aware of the possibility of breakthrough candidemia and echinocandin resistance in patients receiving echinocandin therapy. In such cases, an antifungal susceptibility test followed by molecular screening for FKS mutations would facilitate treatment decisions.

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Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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