Letter to the Editor
Clinical Microbiology

Ann Lab Med 2017;37:556-558
https://doi.org/10.3343/alm.2017.37.6.556
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

First Case of Echinocandin-Resistant *Candida albicans* in Korea

Min-Seung Park, M.D.[1], Jong Eun Park, M.D.[1], Dong Joon Song, M.T.[1], Hee Jae Huh, M.D.[1], Silvia Park, M.D.[2], Cheol-In Kang, M.D.[3], Jong Hee Shin, M.D.[4], and Nam Yong Lee, M.D.[1]

Department of Laboratory Medicine and Genetics[1], Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Division of Hematology-Oncology[2], Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Division of Infectious Diseases[3], Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Department of Laboratory Medicine[4], Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea

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.

Received: February 3, 2017
Revision received: March 20, 2017
Accepted: July 12, 2017

Corresponding author: Nam Yong Lee
Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-2706, Fax: +82-2-3410-2719
E-mail: micro.lee@samsung.com

Co-corresponding author: Jong Hee Shin
Department of Laboratory Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-5342, Fax: +82-62-224-2518
E-mail: shinjh@chonnam.ac.kr

Table 1. Drug susceptibilities of *Candida albicans* isolated in the present case

Method	MIC (μg/mL)/Interpretation*				
	Fluconazole	Voriconazole	Amphotericin B†	Micafungin	Caspofungin
Vitek2 system	16/R	1/R	1	2/R	≥4/R
Broth microdilution method	16/R	16/R	1	>8/R	4/R

*Interpretive criteria used were those published in CLSI document M27-S4 [10]; †No CLSI breakpoint is available.
Abbreviations: MIC, minimal inhibitory concentration; R, resistance.

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 *C. albicans* isolation (day 76), but was then switched to amphotericin B on 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.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1A2B4008181).

Authors' Disclosures of Potential Conflicts of Interest

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

REFERENCES

1. Alexander BD, Johnson MD, Pfeiffer CD, Jiménez-Ortigosa C, Catania J, Booker R, et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of *FKS* mutations and elevated minimum inhibitory concentrations. Clin Infect Dis 2013;56:1724-32.
2. Castanheira M, Messer SA, Rhomberg PR, Pfaller MA. Antifungal susceptibility patterns of a global collection of fungal isolates: results of the SENTRY Antifungal Surveillance Program (2013). Diagn Microbiol Infect Dis 2016;85:200-4.
3. Jang MJ, Shin JH, Lee WG, Kim MN, Lee K, Lee HS, et al. In vitro fluconazole and voriconazole susceptibilities of *Candida* bloodstream isolates in Korea: use of the CLSI and EUCAST epidemiological cutoff values. Ann Lab Med 2013;33:167-73.

4. Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts; Approved Standard. CLSI document M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute 2008a. 2008;28:6-12.
5. Slater JL, Howard SJ, Sharp A, Goodwin J, Gregson LM, Alastruey-Izquierdo A, et al. Disseminated Candidiasis caused by *Candida albicans* with amino acid substitutions in *Fks1* at position Ser645 cannot be successfully treated with micafungin. Antimicrob Agents Chemother 2011; 55:3075-83.
6. Shields RK, Nguyen MH, Press EG, Cumbie R, Driscoll E, Pasculle AW, et al. Rate of FKS mutations among consecutive *Candida* isolates causing bloodstream infection. Antimicrob Agents Chemother 2015;59: 7465-70.
7. Cho EJ, Shin JH, Kim SH, Kim HK, Park JS, Sung H, et al. Emergence of multiple resistance profiles involving azoles, echinocandins and amphotericin B in *Candida glabrata* isolates from a neutropenia patient with prolonged fungaemia. J Antimicrob Chemother 2015;70:1268-70.
8. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161-89.
9. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frêre P, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant 2011;46:709-18.
10. Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts; Fourth Informational Supplement. CLSI document M27-S4. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.

https://doi.org/10.3343/alm.2017.37.6.556