Infectious endocarditis caused by Candida glabrata: evidence of in vivo development of echinocandin resistance

Sir,

Candida glabrata is a major agent of invasive candidiasis and its incidence is on the rise [1]. Overall rates of echinocandin resistance among C. glabrata blood isolates vary according to region, ranging from <1% in Europe to over 10% in some hospitals located in the United States of America [1]. These isolates usually harbor mutations in hot spot regions of the FKS genes, which confer resistance after long-term exposure to echinocandins [1, 2]. Moreover, there is an additional concern regarding C. glabrata strains because of their capacity of rapidly acquiring antifungal resistance during treatment [3].

Candida endocarditis is an infrequent entity, being C. glabrata specifically responsible for about 0.2% of all cases of infectious endocarditis [4]. Despite its low prevalence, Candida endocarditis remains a difficult-to-treat infection, entailing a poor prognosis for most patients [5]. Furthermore, infections by strains with FKS mutations are independently associated with treatment failure and even higher mortality rates [3]. To the best of our knowledge, this is the first report of endocarditis caused by a strain of C. glabrata that acquired resistance to echinocandins during treatment.

An 80-year-old male with a prosthetic aortic valve replacement in 2011 was admitted in December 2015 due to a community acquired pneumonia. He responded well to treatment but remained hospitalized because of recurrent episodes of gastrointestinal bleeding. By March, he presented with fever, diarrhea, and positive blood cultures for Clostridium perfringens and Candida glabrata. Antibiotics and intravenous fluconazole 400mg/day were started adjusted to renal function, which recovered shortly. Abdominal perforation was excluded and the imaging screening for infection source was unremarkable. The patient had a favorable clinical response, being discharged after two weeks of fluconazole at the same dose.

In June, he was re-admitted with fever and hyporexia for over a month. Blood cultures were drawn, yielding a recurrent C. glabrata. Micafungin 100 mg/day was initiated, and follow-up blood cultures were sterile after five days. Nevertheless, the transesophageal echocardiogram (TEE) showed prosthetic aortic valve endocarditis and aortic abscess. The dose of micafungin was increased to 150 mg/day and combined with fluconazole 400 mg/day. Although surgical debridement was recommended, conservative management was preferred due to the patient’s high operative risk.

Within a month of antifungals, he presented clinical signs of treatment failure with severe aortic valve deterioration, requiring urgent valve replacement. Heart valve cultures yielded two morphologically different strains of C. glabrata, being one of them phenotypically resistant to echinocandins. Treatment was switched to liposomal amphotericin B (3 mg/kg/day) combined with fluconazole 800mg/day. Unfortunately, the patient acquired a ventilator-associated pneumonia due to Pseudomonas aeruginosa a week after surgery and died of refractory septic shock.

The antifungal susceptibility results of all Candida isolates were performed according to EUCAST Edif 7.3 [6] and are summarized in table 1. Hot spots 1 and 2 of the FKS1 and FKS2 genes were sequenced and the isolate showing resistance to echinocandins harbored a point mutation in the FKS2 gene. There were two C. glabrata strains from blood culture and two morphologically different strains from the heart valve culture. Nevertheless, all of them proved to be identical after microsatellite genotyping [7], which suggests secondary acquisition of resistance during treatment. Also, all C. glabrata isolates were tested in a Galleria mellonella model [7] and showed no differences in terms of growth kinetics or virulence (data not shown).
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Endocarditis, should have antifungal susceptibility testing of all invasive isolates to promptly detect resistant strains.

Even though echinocandins are highly active against Candida biofilms, infections with a high microbial burden in sites of poor drug penetration may contribute to the emergence of resistant strains [1]. In addition, biofilm formation creates an ideal environment to harbor resistant mutants [12]. This could explain why one of the isolates from the heart valve acquired an FKS2 mutation, whereas those from blood – where the concentration of micafungin is much higher – remained fully susceptible to antifungals. In this context, high-dose echinocandin combined with liposomal amphotericin B could have been more effective against biofilm formation, potentially avoiding the development of echinocandin resistance [13]. Furthermore, C. glabrata strains with FKS mutation seem to have a fitness cost and may regain full susceptibility to echinocandins after treatment with echinocandins is suspended [14]. Thus, improving antifungal prescribing practices may contribute to prevent the development and the spread of resistant clones [14].

In conclusion, we describe a case of recurrent candidemia by C. glabrata complicated with endocarditis by a strain that developed resistance to echinocandins during treatment. This report highlights the importance of performing antifungal susceptibility testing of all invasive isolates to pursue the development of resistance.
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Diagnosis of resistant mutants. Moreover, antifungal stewardship programs are warranted to optimize therapeutic management and thus, prevent the development of resistant strains.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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