Successful treatment of *C. auris* shunt infection with intraventricular caspofungin

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**A B S T R A C T**

*C. auris* is an emerging fungal pathogen with high prevalence of resistance to current antifungal agents. Central nervous system infection with *C. auris* has been infrequently described. We describe here an adult with nosocomial CSF shunt infection due to multi drug resistant *C. auris*. Systemic therapy with echinocandin and fluconazole failed. Fortunately, administration of daily intraventricular caspofungin 10 mg for 10 days in conjunction with systemic voriconazole resulted in both clinical and microbiological cure.

1. Introduction

*C. auris* was first described in an external ear sample of a Japanese patient in 2009 [1]. Since then, the fungus has been reported from numerous countries across the five continents as causing invasive infections and outbreaks in health care facilities [2,3]. Chakrabarti et al. have reported 5.2% of candidemia in Indian ICUs due to *C. auris* [4]. In the author's own institution, four of seven cases of nosocomial candidemia in 2017 were due to *C. auris* (unpublished data). CDC (Centers for Disease Control & Prevention) of USA, Public Health of England, ECDC (European Centre for Disease Prevention and Control) of Europe and Indian Council of Medical Research have issued advisories, which is the first for any fungal disease [5–7].

*C. auris* is phylogenetically related to *C. haemulonii* and *C. ruelliae*. It is commonly misidentified as *Candida haemulonii*, *C. famata*, *C. lusitaniae*, *C. parapsilosis*, *C. sake*, *Cryptococcus laurentii*, *Rhodotorula glutinis*, *Saccharomyces cerevisiae* by conventional laboratory testing [5]. Accurate identification is possible by the VITEK MS or MALDI TOF MS systems or by DNA sequencing. The VITEK 2 system’s database has now been upgraded to identify *C. auris* [8]. In the absence of these systems, growth of the fungus at 37–42 °C, inhibition by cycloheximide, utilization of dextrose, dulcitol and mannitol, formation of pink colonies on chromogenic agar and multidrug resistance should make one suspect *C. auris* [2]. Risk factors for *C. auris* infection are similar to those for other candida species. In a study in Indian ICUs by Rudramurthy et al. patients with *C. auris* were more likely to have longer prior hospitalization, vascular surgery, antifungal exposure, low APACHE 2 scores and coexistent respiratory disease as compared to patients with other Candida species [9]. *C. auris* mostly causes fungemia but sometimes other nosocomial invasive infections. Tentative breakpoints for susceptibility testing for *C. auris* have been proposed by the CDC [5]. The fungus is multi drug resistant with almost universal resistance to fluconazole and variable susceptibility to other azoles and amphotericin B. Echinocandins are the drugs of choice for empiric and definitive therapy but resistance due to mutations in the FKS gene have been reported [9]. Four percent of all isolates have been reported as resistant to all available antifungal agents [8]. Mortality rates have ranged from 28% to 66% across different studies [2]. *C. auris* has this unique ability to colonize hosts, health care workers and hospital environment for prolonged periods thus causing outbreaks [8]. Control measures involve screening for colonization in close contacts of infected patients, placing colonized and infected patients under strict contact isolation thorough environmental cleaning with disinfectants such as hypochlorite and decolonization of infected/colonized hosts with chlorhexidine soap [10].

We describe here a patient who developed a recalcitrant *C. auris* CNS shunt infection was successfully treated with intraventricular caspofungin when conventional systemic therapy failed.

2. Case

A 58 year old with history of ischemic heart disease and bypass
grafting 15 years ago presented with sudden onset of altered sensorium following a right basal ganglia bleed with intraventricular extension. He underwent a right burr hole craniotomy and an external ventricular drainage (EVD) of the right ventricle. Three days later he developed high fever and was empirically put on meropenem and vancomycin for drainage (EVD) of the right ventricle. Three days later he developed hemorrhage. Contrast MRI showing meningitis, ventriculitis and intraventricular hemorrhage.

Fig. 1. Contrast MRI showing meningitis, ventriculitis and intraventricular hemorrhage.

Seven weeks after admission (day +49) and nearly 3 weeks after insertion of shunt, the patient again developed fever and decline in sensorium. The urine and tracheal cultures grew carbapenem resistant *Klebsiella pneumoniae*. Around 4 weeks after admission (Day +28), there was a sudden decline in the patient’s sensorium and the repeat CT showed an increase in ventricular size. A ventriculoperitoneal shunt was inserted with perioperative prophylaxis.

Seven weeks after admission (day +49) and nearly 3 weeks after insertion of shunt, the patient again developed fever and decline in sensorium. A shunt tap was done which was suggestive of a shunt infection. The urine and tracheal cultures grew carbapenem resistant *Klebsiella pneumoniae*. Around 4 weeks after admission (Day +28), there was a sudden decline in the patient’s sensorium and the repeat CT showed an increase in ventricular size. A ventriculoperitoneal shunt was inserted with perioperative prophylaxis.

The treatment of the intracranial infection was a challenge since the most effective drugs against *C. auris*, the echinocandins do not have adequate CNS penetration [11]. This lead to the repeated isolation of Candida despite systemic echinocandin and flucytosine therapy. Interpretation of the antifungal susceptibility reports for the *C. auris* isolate is also difficult since no breakpoints have been established, there is poor agreement between various systems (both microdilution, VITEK 2 and E test) in determining MICs and that voriconazole MICs have shown bimodal/trimodal distributions [12,13]. For these reasons voriconazole even with its MIC of 1 by VITEK 2 (with suggested MIC 50 of 0.5–2) and its good CNS penetration could not be relied upon for therapeutic success. Besides the azoles have very high MIC for biofilm organisms and are less effective when a foreign device (in this case the EVD) is in situ [14].

Treatment of intracranial infections with multidrug resistant pathogens with intrathecal/ intraventricular therapy is well established [15]. Therefore, treatment with local intraventricular caspofungin therapy was instituted which was safe, well tolerated and efficacious. However, the relative contribution of voriconazole and intraventricular caspofungin in therapeutic success in the index case cannot be delineated. Intravitro synergy of echinocandins and azoles against has been recently reported [16].

Soman et al. reported a case of *Candida albicans* shunt associated meningitis which was refractory to therapy with liposomal amphotericin B and flucytosine despite invitro susceptibility where instillation of 10 mg of caspofungin through the Omaya reservoir for 3 weeks resulted in clinical/ microbiologic cure [17]. Murch et al. have also reported successful therapy of multiple Pseudallescheria boydii brain abscesses and ventriculitis/ependymitis in a 2-year-old child after a near-drowning episode with intraventricular caspofungin [18]. Williams et al. recently reported use of intraventricular caspofungin 5 mg in a patient with Scedosporium apiospermum CNS infection following spine surgery who failed therapy with voriconazole and terbinafine. Treatment was well tolerated and resulted in clinical improvement and
sterilization of the CSF; unfortunately progression of disease occurred after withdrawal of therapy leading to death [19].

With the growing menace of C. auris, we are likely to see increase in intracranial infections due to this pathogen as well. Owing to inherent resistance of this fungus against antifungal agents with good CNS penetration, the safety, optimum dosage/formulation and efficacy of intraventricular echinocandin therapy needs to be investigated further.

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Conflict of interest

There are none.

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