Case Report

Resistant invasive *Candida auris* reported in neutropenic patients treated successfully with three antifungals

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ABSTRACT

Candida auris is a deadly fungal pathogen able to cause fatal symptoms in immunocompromised patients. It may be misidentified and difficult to clinically diagnose. The guidelines are to employ Echinocandin and Amphotericin B in the treatment, but the following study elucidates successful treatment of infection by a combination of three classes of antifungal drugs; never reported before. We present a patient with fulminant acute disseminated encephalomyelitis and neutropenia who developed invasive candidiasis despite appropriate antifungal therapy. We successfully treated ongoing candidemia with three antifungal drugs which lead to the resolution of fungemia after 18 days of treatment. Isolation, segregation, waste disposal, and deep cleaning technique were also followed as recommended by the Infectious Diseases Society of America guidelines. First report of Candidemia in an immunocompromised patient was successfully treated with three classes of antifungal drugs, IV Micafungin, Amphotericin B, and Posaconazole for nearly 18 days.

Key words: Amphotericin B, Micafungin, Posaconazole, Candidemia, Neutropenia, Immunocompromised

Candida auris is a rare emerging fungal pathogen, associated with neutropenia and high mortality. The prevalence of *C. auris* has been reported to be ranging from 5% to 30% of all candidemia cases in certain hospitals [1,2]. It is thought to be the new global threat to public health. The difficulty and usual misidentification in the clinical diagnosis of *C. auris* contributes to the threat factor. It is known to be multidrug-resistant (MDR), some strains being resistant to all three classes of available antifungals and capable of causing an outbreak in the hospital if not handled effectively.

In the given case, the patient suffered from neutropenia, the guidelines are suggestive of treating such a condition with Echinocandin as the initial agent of choice along with Amphotericin B as an alternative drug. However, this study suggests a not-reported treatment approach of combining all three classes of antifungals.

CASE REPORT

A 32-year-old man was admitted with complaints of fever, altered sensorium, headache, and weakness in the left upper limb, which progressed, to nearly flaccid quadriplegia in a few days. A magnetic resonance imaging brain showed a right frontal-cerebral hyperintense lesion of 6.5–7 cm extending to the splenium of the corpus callosum, midbrain and pons, post limb of the internal capsule with mass effect, and effacement of the right lateral ventricle. There were also diffuse T2 hyperintense changes seen in the brainstem involving the white matter pathways in the dorsal region, the cerebral peduncles, and also the ventral tegmentum of the pons and medulla. With negative cultures even of the cerebrospinal fluid for any infection, he was diagnosed with fulminant acute demyelinating encephalomyelitis.

He was treated with immunosuppressive therapy comprising of steroids and plasmapheresis with IV Cyclophosphamide. He had an ongoing fever (temp >101°C, HR-120/min, SBP-123 mmhg, fluctuating GCS, and intubated for airway protection) with subsequent endotracheal cultures growing *Escherichia coli,* for which he was treated with IV Amikacin 750 mg daily and IV Meropenem 1gm thrice daily. 4 days after admission, the patient worsened and developed neutropenia (White blood cells [WBC]-1080 and absolute neutrophil count (ANC)-380) and dilated pupils, which on brain imaging revealed signs of herniation, which were relieved by a bilateral decompressive craniotomy.

Given worsening neutropenia and fever, the antibiotic regimen was escalated to include antiviral and antifungal and Gram-positive

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covers with IV Teicoplanin 400 mg daily, Tab Acyclovir 800 mg thrice daily, and Tab Fluconazole 200 mg daily along with IV Meropenem 1 g thrice daily and Inj. Amikacin 750 mg daily that were continued as per antibiotic sensitivity pattern. The patient remained neutropenic on the 8th day after admission, reached a nadir of neutropenia (WBC-70, ANC-0), developed high-grade fever despite the adequate broad cover, and developed mild liver dysfunction. Repeat endotracheal aspirates grew *C. auris*, which was sensitive to Anidulafungin (Table 1). Corresponding blood culture demonstrated growth of MDR *Escherichia coli,* sensitive only to Colistin, but was negative for *C. auris*. Antibiotic and antifungal regimes were altered to include IV Anidulafungin and Nebulized Colistin along with Meropenem. Indwelling catheters were changed as per unit protocol.

The patient underwent bedside Tracheotomy on the 13th day, considering the need for prolonged ventilation. He remained stable hemodynamically; the neutropenia improved on day 15 of the intensive care unit stay (WBC-8740, ANC-57), and was successfully weaned off from the ventilator support with slow neurological recovery. However, fever persisted despite the treatment, and hence repeat blood and urine cultures were performed. These grew candidemia with *C. auris* (Table 1) despite treatment with susceptible antifungal drugs and necessary infection control measures taken. IV. Amphotericin B, IV. Posaconazole was added with ongoing IV. Anidulafungin was continued along with ceftriaxone- Sulbactum; Daptomycin where as Colistin and Meropenem were discontinued. Barrier isolation, waste segregation, health-care personnel decontamination, and deep cleaning with 2% hypochlorite solution were undertaken as per the infection control protocol. The patient continued to have fever spikes intermittently; hence Anidulafungin was switched to IV. Micafungin on day 26. He was treated with three antifungals (Amphotericin B, Micafungin, and Posaconazole) for nearly 18 days. Gradually, he showed clinical improvement., Previously elevated WBC gradually returned to normal, levels of fever subsided, and he was decannulated and discharged home on day 31 (Fig. 1).

DISCUSSION

This is a case report depicting candidemia in an immunocompromised patient in Mumbai, India. In Japan, in 2009 the first case of *C. auris* was described and since then has been reported in many countries [3]. Infections due to *C. auris* are MDR, usually, hospital-acquired, and associated with high mortality as high as 70% and maybe even higher in case of candidemia with neutropenia [4-6]. In South America, it is the sixth most common cause of bloodstream infection [7].

Early identification of *C. auris* is difficult by conventional techniques. However, once identified it is important to effectively treat it. One must suspect *C. auris* when an isolate is identified of other *Candida* species such as *Candida haemuloni*, *Candida famata*, and *Rhodotorula glutinis* or the identification of the species is not possible. Rapid, efficient, and successful identification of *C. auris* are usually shown by Vitelli MS and the MALDI-TOF identification system [8,9].

According to the Indian Council of Medical Research 2017, the overall resistant pattern of *C. auris* is seen as resistance to Fluconazole >90%, Voriconazole ~50%, Amphotericin B >30%, and Echinocandin ~7–10%. According to the Infectious Diseases Society of America (IDSA) guidelines 2016, antifungal susceptibility testing should be recommended in clinically relevant *Candida* isolates. Resistance to more than one antifungal drug in isolates should raise the suspicion of *C. auris* and prompt

Table 1: Susceptibility of *Candida auris* after admission on day 8 in endotracheal secretion and on day 18 in blood and urine culture

Susceptibility of *Candida auris*	Antimicrobial Agent	Interpretation	MIC value (µg/ml)
On day 8 in endotracheal secretion (10^4 cfu/ml)	Amphotericin B	Resistant	>=16
	Flucytosine	Resistant	>=64
	Voriconazole	Resistant	4
	Caspofungin	Resistant	0.25
	Micafungin	Resistant	0.12
	Anidulafungin	Sensitive	0.002
	Fluconazole	Resistant	32
On day 18 in blood culture (10^3)	Amphotericin B	Resistant	8
	Fluconazole	Resistant	32
	Voriconazole	Susceptible	1
	Caspofungin	Susceptible	0.25
	Micafungin	Susceptible	0.12
	Anidulafungin	Susceptible	0.12
On day 18 in urine culture (10^3)	Amphotericin B	Resistant	8
	Fluconazole	Resistant	32
	Voriconazole	Resistant	4
	Caspofungin	Susceptible	0.25
	Micafungin	Susceptible	0.12
	Anidulafungin	Susceptible	0.12

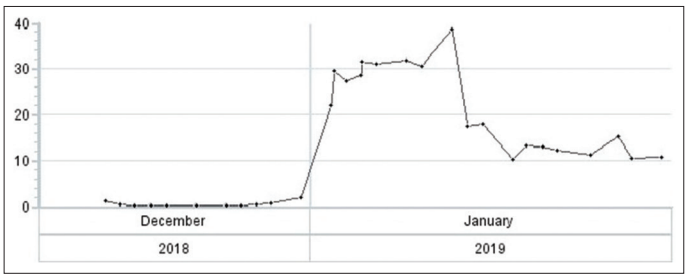

Figure 1: White blood cell trends throughout the hospital stay

further testing [6]. According to the current IDSA guidelines for the treatment of candidemia with or without neutropenia, Anidulafungin and Micafungin under the Echinocandin group remain the first-line therapy along with infection prevention control strategy [10]. Also according to the Centers for Disease Control and Prevention (CDC) recommendations, further switching to liposomal Amphotericin B could be considered if the patient is clinically unresponsive to Echinocandin therapy or has fungemia for more than 5 days [10,11].

We treated this case of fulminant ADEM with severe neutropenia who later developed candidemia, despite susceptible Echinocandin therapy. Candidemia was treated with three classes of antifungal drugs, which included IV Micafungin, Amphotericin B, and Posaconazole for nearly 18 days. Treatment of candidemia in an immunosuppressed individual with three different classes of antifungals has not been previously reported in the literature. Hence, this could be considered a new regimen of treatment for such patients. The positive outcome of treatment in our patient ratifies this treatment approach. Our patient improved clinically, fever subsided, WBC became normal and the patient was discharged with minimal residual neurological weakness.

CONCLUSION

The persistent invasive MDR candidemia with *C. auris* infection in an immunocompromised patient can be treated successfully with a combination of three classes of antifungal drugs.

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