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Case Report

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A case developing *Candida auris* related candidaemia following multiple drug-resistant *Klebsiella pneumoniae* meningitis after neurosurgical intervention

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ABSTRACT

A 28-year-old man who underwent ventriculoperitoneal shunt (VPS) operation at another medical center due to epidural abscess and hydrocephalus was admitted due to deterioration of his general condition. He was receiving vancomycin and meropenem treatment for epidural abscess. Urine cultures were taken during hospitalization and again 48 hours later and *Candida auris* (*C. auris*) growth of 10^5cfu/ml was detected. On the 4th day of hospitalization, the patient was intubated due to decreased oxygen saturation, and while under meropenem and vancomycin treatment, carbapenem-resistant, gentamicin and ceftazidime-avibactam-susceptible and multidrug-resistant *Klebsiella pneumoniae (K. pneumoniae)* growth was detected in CSF culture. The patient's VPS was removed and hydrocephalus was followed with extra-ventricular drainage (EVD). Vancomycin treatment was discontinued and intrathecal (IT) gentamicin treatment was started. Due to the susceptibility of *K. pneumoniae* growth from deep tracheal aspirate to ceftazidime-avibactam, antibiotic treatment was changed to intravenous (IV) meropenem, IV ceftazidime-avibactam and IT gentamicin and treatment was continued for 10 days. On the 20th day of hospitalization due to deterioration of his clinical condition under treatment, tracheostomy was performed, he was intubated, blood and urine cultures were repeated and *C. auris* growth was detected in blood culture on the 27th day after hospitalization using VITEK MS MALDITOF (bioMérieux, France) microbiological identification system. Confirmation of the *C. auris* species and antifungal susceptibility testing was performed by the Mycology Reference Laboratory, Institute of Public Health and antibiotic treatment was stopped. According to the antifungal susceptibility test results, the patient was started on anidulafungin. In conclusion, nosocomial *C. auris* infection should be considered in patients with underlying predisposing factors such as long intensive care unit stays, broad-spectrum antibiotic use, surgical interventions, central venous catheter use, intubation and infection due to gram-negative bacteria.

Keywords: Nosocomial meningitis, multidrug-resistant, *Klebsiella pneumoniae*, *Candida auris*, candidemia

INTRODUCTION

Post-neurosurgical meningitis (PNM), a complication with a high mortality rate, may develop after neurosurgical interventions. The most common bacteria causing PNM are *Acinetobacter baumannii* and *Klebsiella pneumoniae (K. pneumoniae)*.[1] PNM due to multidrug-resistant (MDR) *K. pneumoniae* has a high mortality rate if not treated appropriately.[2]

In recent years, cases of nosocomial *Candida auris* (*C. auris*) have been reported in patients hospitalized in intensive care units (ICUs) with underlying predisposing factors.[3-6] *C. auris* is an important *Candida* species that can show multiple antifungal resistance and is frequently identified by molecular methods.[7-10] In this article, we report a 28-year-old male patient who developed fungemia and candiduria due to *C. auris* following meningitis due to MDR *K. pneumoniae* after neurosurgical surgery.

CASE

A 28-year-old male patient who underwent ventriculoperitoneal shunting (VPS) due to epidural abscess and hydrocephalus

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in another healthcare institution was admitted to the ICU of brain and nerve surgery due to deterioration in general condition. It was learned from his epicrisis that he had been operated on three years ago for subdural hematoma and underwent cranioplasty. It was learned from his epicrisis that he was operated on for right parenchymal hematoma in the brain after a motor vehicle accident approximately 2 years after this operation, and VPS was performed in another healthcare institution due to the development of hydrocephalus, and vancomycin and meropenem treatment was administered for 30 days. On physical examination at the time of admission to the ICU of brain and nerve surgery, the general condition was moderate, consciousness was blurred, the Glasgow coma score was 12, the patient was extubated, and the patient was receiving oxygen therapy with a mask due to respiratory distress. Pupils were isochoric, and light reflex was present. The patient had left hemiplegia and a stage 2 sacral decubitus ulcer. Laboratory tests revealed a leukocyte count of 9360/mm^3, C-reactive protein (CRP) of 54 mg/L (normal <5 mg/L), a glomerular filtration rate of 150 ml/min, and other laboratory tests were normal. The patient was consulted in the infectious diseases department in the brain and nerve surgery ICU, and treatment with vancomycin and meropenem was continued. Urine culture taken on the day of hospitalization showed >10^5 cfu/ml *C. auris* growth after 48 hours, and there was no significant growth in blood and catheter cultures. On the 4th day of hospitalization, the patient was intubated due to decreased oxygen saturation (SpO_2<75). Blood, intracatheter blood, cerebrospinal fluid (CSF), and rectal swab cultures were obtained from the patient whose CRP value was found to be increased. There was no growth in blood and intracatheter blood cultures. Vancomycin-resistant enterococci (VRE) were grown in the rectal swab sample, and contact isolation measures were applied. While under meropenem and vancomycin treatment, carbapenem-resistant, MDR *K. pneumoniae* susceptible to gentamicin and ceftazidime-avibactam was grown in CSF culture. VPS was removed, and hydrocephalus continued to be monitored with extra ventricular drainage (EVD). Vancomycin treatment was discontinued, and IT gentamicin treatment was started. Upon the growth of *K. pneumoniae* susceptible to ceftazidime-avibactam in deep tracheal aspirate culture, the patient's treatment was adjusted to meropenem intravenous (IV), ceftazidime-avibactam (IV), and gentamicin IT. Treatment was administered for 10 days. There was no growth in the CSF culture obtained under treatment, the cell count in CSF was normal, and the patient's EVD was withdrawn. On the 20th day of hospitalization, the patient's clinical findings worsened under treatment, tracheostomy was opened, and the patient was intubated; blood and urine cultures were repeated. *C. auris* was grown in the urine culture obtained during hospitalization and in the blood culture obtained on the 27th day of hospitalization. *C. auris* grown in urine culture was not considered an infectious agent. *C. auris* grown in blood culture was identified by the VITEK® MS MALDI-TOF (BioMérieux, France) microbiologic identification system. Confirmation of the *C. auris* strain grown in blood culture and antifungal susceptibility tests were performed by Mycology Reference Laboratory. Existing antibiotic treatments were discontinued. Susceptibilities of *C.auris* strains to amphotericin B, azoles (fluconazole, itraconazole, voriconazole, posaconazole), and echinocandins (anidulafungin, micafungin, caspofungin) were studied by liquid microdilution according to CLSI M27-A3. MIC values obtained as a result of the antifungal susceptibility study of the strain isolated from blood; amphotericin B: 1 (µg/ml), voriconazole: 0.25 (µg/ml), caspofungin: 0.5 (µg/ml), posaconazole: 0.5 (µg/ml), fluconazole: 256 (µg/ml), itraconazole: 0.5 (µg/ml), anidulafungin: 1(µg/ ml). Anidulafungin treatment was started according to the antifungal susceptibility results. The patient's medical devices were separated, contact isolation measures and infection control measures were applied. Following the treatment, daptomycin was added to the patient's treatment with the diagnosis of catheter infection due to the growth of *Staphylococcus haemolyticus* in blood and intracatheter blood cultures. Anidulafungin and daptomycin treatment was administered for 14 days, and the central venous catheter was withdrawn. After treatment, the patient's general condition improved, and he was transferred from the ICU to the brain and nerve surgery service. No pathologic findings developed except for left hemiplegia, which was detected at the beginning. The patient was discharged for follow-up.

DISCUSSION

PNM is an important and life-threatening complication of neurosurgical operations. The most frequently reported PNM agents in the literature are *Acinetobacter baumannii* and *K. pneumoniae*.[1,2] Iaria et al.[1] evaluated the results of intraventricular colistin treatment in five patients who developed PNM due to MDR gram-negative bacteria in a study conducted in Italy. In the study, MDR *Acinetobacter baumannii* and MDR *K. pneumoniae* were isolated in four and one case, respectively. Intraventricular colistin treatment was administered for a median of 18 days, and IV meropenem and colistin treatment was administered together with intraventricular colistin in all cases. Four of the patients recovered with treatment and were discharged, while one patient died as a result of respiratory complications. Patrial et al.[2] also reported two cases of PNM due to carbapenem-resistant *K. pneumoniae*. In these cases, it was reported that *K. pneumoniae* strains had extended-spectrum beta-lactamase enzymes together with KPC enzymes responsible for carbapenem resistance. The cases were successfully treated with IT polymyxin B followed by I.V. meropenem therapy. Sreejith et al.[11] reported a 26-year-old male patient who developed pneumocephalus as a complication of meningitis due to MDR *K. pneumoniae* as a complication of chronic suppurative otitis media.

In the present case, MDR *K. pneumoniae* was isolated as the causative agent of PNM. Since the isolated strain was susceptible to gentamicin, IT gentamicin and meropenem treatment was started by the IV route. After 10 days of treatment, there was no growth in CSF culture. In the present case, *C. auris* was grown in the urine culture obtained during hospitalization and in the blood culture obtained on the 27th day of hospitalization.

Our case is interesting because it is the first case of candidiasis due to *C. auris* following PNM due to MDR *K. pneumoniae* and the first case of *C. auris* reported in our hospital. According to the English literature, our case is the first case of *C. auris* infection following PNM due to *K. pneumoniae*. *C. auris* is a hospital-acquired *Candida* species

that has been the focus of attention in the world and Turkiye in recent years. *C. auris* was first reported in 2009.[6] *C. auris* is an important opportunistic pathogen because it causes outbreaks as well as nosocomial infections, is resistant to antifungals and disinfectants, and cannot be identified by current conventional identification systems.[3,5,12]

The fact that *C. auris* can easily spread among patients and between hospitals, cause epidemics, survive on surfaces for a long time, and show multiple antifungal drug resistance has caused concern all over the world.[3,5,12,13] Garcia et al.[12] reported an outbreak due to *C. auris* between 2017 and 2019 in their study conducted in Spain. In the study, it was reported that a total of 203 patients were colonized or infected with *C. auris*, and invasive *C. auris* infection developed in 30 patients (candidemia in 29 cases and meningitis in one case). The causative agent was determined to be *C. auris* in 32% of cases with candidemia, and all *C. auris* isolates were fluconazole resistant. In the *C. auris* strain isolated in the present study, high fluconazole minimal inhibitory concentration (MIC) values (≥256 mg/ml) were found, while MIC values for other antifungals were low.

In the literature, it has been reported that 60-90% of *C. auris* strains are resistant to fluconazole, 10-30% have high minimum inhibitory concentration values for amphotericin B, and approximately 5% are resistant to echinocandins.[13] Today, outbreaks due to *C. auris* have been reported in hospitals in many countries.[4,12] Thoma et al.[5] reported an outbreak due to carbapenem-resistant MDR *A. baumannii* and *C. auris* in the COVID-19 pandemic. In the study, lack of personal protective equipment, hand hygiene, and use of personal protective equipment were reported as the most frequently reported potentially modifiable factors contributing to outbreaks. Bölükbaşı et al.[4] reported a 71-year-old male patient with underlying lung cancer and diabetes who developed fungemia due to *C. auris* after COVID-19 infection.

The patient was started on immunosuppressive corticosteroid and tocilizumab treatments for COVID-19 pneumonia. The *Candida* strain grown in the patient's blood culture was identified as *C. auris* by the VITEK MS MALDI-TOF system and confirmed by sequence analysis. The isolated *C. auris* strain was fluconazole resistant and susceptible to amphotericin B, anidulafungin, caspofungin, itraconazole, and posaconazole. Despite caspofungin and broad-spectrum antibiotic treatment, the patient died on the ninth day of treatment. Based on this case, the authors recommended caution in terms of *C. auris* infections, especially in ICUs. The main reasons for the increase in *Candida* infections are the increase in the number of immunosuppressive patients, the use of broad-spectrum antibiotics, and the widespread use of invasive interventions (central venous catheter, urinary catheter, tracheostomy, etc.).[6,14]

Broad-spectrum antibiotic use, immunosuppressive agents, and catheterization are among the predisposing factors for *C. auris* infection.[5,6] Kömeç et al.[6] reported a *C. auris*-related infection in three patients hospitalized in the ICU in İstanbul. The common features of the three cases reported were that they were ICU intubated patients, they had central venous catheters, they used broad-spectrum antibiotics, and they were reported as infections due to MDR bacteria. In all seven cases of *C. auris* reported from the United States, hematologic malignancy, bone marrow transplantation, central venous catheterization, and urinary catheterization were reported as predisposing factors.[6,16] In our case, the main risk factors were the use of broad-spectrum antibiotics, meningitis due to MDR *K. pneumoniae*, the presence of a urinary catheter, a central venous catheter, EVD, and the patient being ventilator dependent. Automated systems used in routine diagnosis are insufficient in identifying *C. auris* or may lead to erroneous definitions.[6,13]

The three isolates identified as *C. auris* by Kömeç et al.[6] by MALDI-TOF Microflex LT/SH Smart MS were confirmed by conventional methods and DNA sequence analysis at the National Mycology Reference Laboratory. By the liquid microdilution method, all three isolates were reported to be fluconazole resistant (MIC) values (>256 mg/ml). *C. auris* can cause nosocomial infections and outbreaks because it can survive for a long time in hospital environments. Therefore, *C. auris* is of nosocomial origin.[3,4] In addition, the fact that it can colonize on the skin and is resistant to disinfectants facilitates its spread. Its high rate of resistance to antifungal drugs leads to treatment failures.[4,13] With the case we presented, we aimed to draw attention to the infections caused by *C. auris*, its diagnosis, and risk factors. *C. auris* can be erroneously identified by routine laboratory methods, the VITEK-2 automated system, and API systems. Therefore, confirmation of *Candida* isolates by MALDI-TOF MS or DNA sequence analysis is recommended.[6,7,15] In our case, *C. auris* was identified by VITEK® MS MALDI-TOF (BioMérieux, France) and confirmed by DNA sequence analysis at the Public Health Mycology Reference Laboratory.

Karabıçak et al.[7] found fluconazole resistance in 70 *C. auris* isolates isolated from various hospitals in Turkiye (MIC50 and MIC 90 ≥256mg/ml) by the liquid microdilution method, while the identification of the isolates was identified by MALDI-TOF MS, and the sequence analysis of the isolates was 100% compatible with *C. auris*. Kulaklı et al.[8] reported *C. auris* in tissue culture in a 59-year-old male patient who underwent below-knee amputation due to diabetic foot infection. *C. auris* was identified by MALDI-TOF MS. The MIC value of *C. auris* isolate was reported as >64 µg/ml for fluconazole, 2 µg/ml for amphotericin B and 0.25 µg/ml for caspofungin. It was reported that the case was the first case of *C. auris* reported from İzmir province, and there was no growth in the culture performed again from the amputation site after antifungal treatment. Patient-directed infection control measures were taken to prevent interpatient transmission. In the present case, the patient's medical instruments were separated, contact isolation was performed, and infection control measures were taken. Aslan et al.[9] isolated *C. auris* from urine and blood cultures in an 89-year-old female patient receiving treatment for ventilator-associated pneumonia in ICU. The isolated *C. auris* was identified by MALDI-TOF MS and confirmed by sequence analysis. When fluconazole MIC value was found to be 16 mg/ml in the *C. auris* isolate, amphotericin B treatment was started according to the antifungal susceptibility result, contact isolation was performed, and infection control measures were taken. Öncel et al.[10] reported that 10 (6.3%) of a total of 157 *Candida* spp. isolated from ICU inpatients were *C. auris* in their study conducted in İstanbul. The most frequently isolated *Candida* species was reported as *Candida albicans* with 60 (38.2%) isolates. In the study, it was reported

that *C. auris* strains had high MIC values for amphotericin B, fluconazole, itraconazole, voriconazole, and posaconazole by the liquid microdilution method and showed multidrug resistance.

Özalp et al.[17] reported the *Candida* species isolated from a total of 217 patients in their retrospective study investigating *Candida* species causing bloodstream infections between 2020 and 2011 as *Candida albicans* 37.8%, *C. parapsilosis* 17.1%, *C. glabrata* 15.2%, *C. tropicalis* 15.2% and *C. auris* 9%, respectively. Candidemia developed in 175 (81.4%) patients during hospitalization in the ICU. Mortality was reported in 114 (52.3%) patients in the study group, and mortality rates were lower in patients infected with *C. parapsilosis* or *C. auris*. Age and previous COVID-19 infection were identified as risk factors for candidemia.

The 2022 SENTRY Antifungal Surveillance Program has been reported a significant increase in the prevalence of *C. auris* among invasive candidiasis isolates compared to previous years (≤0.1% before 2018, 0.4%-0.6% from 2018 to 2021 and 1.6% in 2022). The study included 28 (35.9%) *C. auris* isolates from the USA, 26 (33.3%) from Panama, and 12 and 9 isolates from Greece and Turkiye, respectively. Of all isolates, 82.1% were resistant to fluconazole, 17.9% to amphotericin B and 1.3% to caspofungin, anidulafungin or micafungin. Pan-drug resistance has not observed, but 17.9% of isolates were reported to be resistant to fluconazole and amphotericin B.

CONCLUSION

As a result, it should be kept in mind that nosocomial *C. auris* infection may be seen in patients with predisposing factors such as long-term hospitalization in the ICU, underlying broad-spectrum antibiotic use, surgical intervention, central venous catheter use, intubation, and infection due to MDR gram-negative bacteria.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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