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The Second Case of *Candida auris* Candidemia from Turkey: An Impending Threat to the Global Health

Türkiye'den İkinci *Candida auris* Sepsisi Olgu Sunumu: Küresel Sağlık için Yaklaşan Bir Tehdit

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Abstract

Candida auris is a rapidly emerging fungus which is globally considered as a cause of public health concern. This report describes Turkey's second case of *Candida auris* fungemia from a tertiary care hospital in İstanbul. An 18-year-old male patient with a brain cancer was presented to the emergency department. Later, *Candida auris* was isolated from the catheter and blood cultures of the patient. Initially, the yeast was misidentified as *Cryptococcus laurentii* using the VITEK-2 system. The isolates were confirmed to be *Candida auris* by means of matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry and DNA sequence analysis. Antifungal susceptibility testing was performed on this isolate, which exhibited high minimum inhibitory concentrations to fluconazole. The patient who received micafungin treatment died. *Candida auris* is a potentially antifungal resistant pathogen, causing healthcare-associated infections and outbreaks. For these reasons, it is necessary to achieve an accurate and quick identification and to implement contact precautions quickly.
Keywords: *Candida auris*, fluconazole, candidemia, intensive care unit

Öz

Candida auris'in küresel anlamda hızla yayılması endişe uyandırmaktadır. Bu raporda, İstanbul'daki üçüncü basamak bir hastaneden Türkiye'nin ikinci *Candida auris* fungemi olgusu anlatılmaktadır. Acil servise başvuran beyin tümörü olan 18 yaşındaki erkek hastanın hem kateter kültüründen hem de kan kültüründen *Candida auris* izole edildi. Maya, başlangıçta VITEK-2 sistemi kullanılarak *Cryptococcus laurentii* olarak yanlış tanımlandı. İzolatların, matris destekli lazer desorpsiyon/iyonizasyon uçuş zamanı kütle spektrometresi ve DNA sekans analizi aracılığıyla *Candida auris* olduğu doğrulandı. *Candida auris* izolatının, flukonazole karşı yüksek minimum inhibitör konsantrasyonuna sahip olduğu saptandı. Mikafungin tedavisi alan hasta öldü. *Candida auris*, potansiyel olarak çoklu ilaca dirençlidir ve hastane kaynaklı salgınlara ve sporadik enfeksiyonlara neden olur. Bu enfeksiyonun doğru ve hızlı bir şekilde tespit edilmesi ve gerekli kontrol ve koruma önlemlerinin hızla alınması gerekmektedir.
Anahtar Kelimeler: *Candida auris*, flukonazol, kandidemi, yoğun bakım ünitesi

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Introduction

Candida auris is a recently described *Candida* species, which is phenotypically and phylogenetically closely related to the *Candida haemulonii* species complex (*Candida pseudohaemulonii* and *Candida haemulonii*). It may be misidentified using the conventional biochemical or commercial methods, and requires specific technology for its identification[1,2]. Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS) and DNA sequencing provides a correct identification[3]. The first report of *C. auris* infections from Turkey with confirmed identification by the MALDI-TOF MS and DNA sequence analysis appeared in the year of 2021[4]. This report describes the second case of *C. auris* fungemia from a tertiary care hospital in Turkey.

Case Report

An 18-year-old male patient with brain cancer presented to the emergency department with the symptoms of fever, dyspnea, and expectoration in November 2020. The patient had two surgeries in 2017 and 2019, after being diagnosed with brain cancer. The patient underwent multiple long-term hospitalizations and received wide-spectrum antibiotic treatment, and several immunosuppressor agents. He had undergone tracheostomy and percutaneous endoscopic gastrostomy nine months prior, during his last hospitalization. On examination, the patient's body temperature was 38.3 °C, blood pressure was 125/80 mmHg, pulse was 120 bpm, and pulse oximeter oxygen saturation at rest was 70% on room air. Purulent secretion in the tracheostomy area and bilateral crepitation rales in the lung bases were detected. His leukocyte level was 13,000/µl, and his C-reactive protein level was high at 139 mg/l. Chest computed tomography revealed lobar pneumonia in the right middle and lower lobe division. The patient was admitted to the intensive care unit (ICU) of our hospital with the diagnosis of lobar pneumonia, and intravenous antibiotic treatment with piperacillin/tazobactam was given for about 10 days. Clinical improvement was achieved with antibiotic therapy, but the need for mechanical ventilator support was continued. Only once during his follow-up in the hospital, the patient diagnosed with hospital-acquired pneumonia caused by *Proteus mirabilis* and received proper antibiotic treatment with meropenem and fosfomycin based on the culture and sensitivity. The patient developed central line-associated bloodstream infection caused by *Acinetobacter baumannii* in the 3rd month of follow-up in the hospital; antibiotic treatment with cefoperazone-sulbactam at a dose 4 g/day and colistin at a dose of 300 mg/day was initiated. The infection parameters decreased significantly and the infection was controlled. However, after a short period of stabilization, he became hypotensive requiring inotropic assistance on the 7th day of this treatment. During examination, the patient was unconscious, and his body temperature was 39.3 °C, blood pressure was 110/65 mmHg, pulse was 95 bpm, and hyperemia over his femoral line catheter side was present. Blood tests revealed a leukocyte count of 15,240/µl, neutrophils of 9380/µl, C-reactive protein of 234 mg/l, and procalcitonin of 0.7 ng/ml. The femoral line was removed, and the catheter was sent for microbiological culture; simultaneously, peripheral blood culture samples were taken. Micafungin at a dose of 100 mg/day and meropenem at a dose of 3 g/day were started, and colistin therapy was continued. However, on the 2nd day of this treatment, the patient's condition deteriorated, and he died.

The catheter sample was identified as *Cryptococcus laurentii* by the VITEK-2 system. This isolate was identified as *C. auris* by the MALDI Bruker (Bruker Daltonics, Germany) and VITEK MS (bioMerieux, Marcy, L'Etoile, France) systems. Blood culture was performed by means of an automated BACT/ALERT 3D Microbial Identification System (bioMérieux) which signaled positive growth after three days of incubation. Blood culture reports revealed the presence of *C. auris* by the VITEK-2 system. On subculture, tiny, white, opaque, non-hemolytic colonies were obtained on 5% sheep blood agar (Figure 1). Gram staining revealed Gram-positive budding yeast cells. The yeast was identified as *C. auris* by MALDI-TOF MS (Bruker Daltonics, Germany) with a score of 2.3 with direct formic acid extraction, and VITEK MS with a score of 99.9%.

The confirmation of the isolate was identified by an ITS sequence analysis. The Biospeedy Fungal DNA isolation kit was used for DNA extraction from an isolate. The amplification of the ITS1-5.8S-ITS2 rDNA region was performed on a CFX Connect real-time polymerase chain

Figure 1. 5% sheep blood agar showing colony appearance of *Candida auris*

reaction (PCR) detection system (Bio-Rad Laboratories, USA). The primer pair 5'-TCC TCCGCTTATTGATATGC-3' forward and 5'-GGAAGTAAAAGTCGTAACAAGG-3' reverse was used for PCR reaction with the following cycling protocol: initial denaturation at 95 °C for 10 min; 40 cycles of denaturation at 95 °C for 15 s, annealing at 52 °C for 15 s; extension at 72 °C for 30 s; melting curve analysis at 95 °C for 5 s, 65 °C for 5s, and 98 °C 5s; and finally, cooling at 40 °C for 30 s. PCR products were purified by the Biospeedy® PCR purification kit. The purified PCR products were employed for cycle sequencing reactions in a forward direction. The sequence of the fungal isolate was analyzed in Chromas software package version 1.45 and evaluated using NCBI BLAST searches against ITS from the fungi type and reference material existing in DNA databases (http://blast.ncbi.nlm.nih.gov/Blast.cgi). If homology with other entries in the database used for the comparison is ≥97%, the result is considered acceptable. Our isolate yielded 98.38% homology with *C. auris* CBS 10913. The sequences of *C. auris* strain have been deposited in GenBank under accession number MW4413141.

In vitro susceptibility was determined by the broth microdilution procedure-based commercial calorimetric Thermo Scientific antifungal susceptibility testing panel (Sensititre™; Thermo Scientific USA) for yeast by following the manufacturer's instructions (Table 1). The institutional infection control committee was informed about the finding. All hospitalized patients who had an epidemiologic link to a case patient or colonized patient in place or time were screened for the isolation of *C. auris*. The surveillance samples were mostly obtained from the axilla, groin, and nose of patients with or without clinical signs of infection. The environmental samples processed in this study were obtained from the rooms/units occupied. Swab samples were obtained from medical instruments, linen, walls/floor, furniture, and high-touch areas, such as a doorknob, bed railings/bedside drawer, and toilet faucet. All clinical samples collected from patients and the environment were processed according to the standard laboratory operational policy. Environmental samples were inoculated on sabouraud dextrose agar containing gentamicin and chloramphenicol. After incubation at 37 °C for 24-48 h, species-level identification of *Candida* isolates was performed by proteomic profiling by MALDI-TOF MS. *C. auris* was not detected in screening cultures. No new cases were detected in the next few months.

Informed consent could not be obtained because *C. auris* infection was diagnosed in the patient's culture after he died. Since screening for the detection of patients colonized with *C. auris* is included in our routine infection control measures, the informed consent form was not obtained from other patients in the ICU.

Discussion

The patient with *C. auris* isolate in this report had similar risk factors to those described in the literature, such as immunosuppressive, use of broad-spectrum antibiotics, hospitalization in the ICU, and urinary catheters[5-7]. All these conditions have been considered as classic risk factors for deep-seated *Candida* infections and candidemia, and some of them for *C. auris* infections. Similar to our case, many publications describing *C. auris* highlight that this species is frequently misidentified[8,9]. According to the literature, API 20C, VITEK-2 (bioMérieux, France), Phoenix (BD), and MicroScan (Beckman Coulter, Pasadena, CA) technologies may misidentify *C. auris* as *Candida haemulonii*, a rare cause of the infection in humans, but also *Candida famata*, *Candida sake*, *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Saccharomyces* species[10]. Misidentification may lead to inadequate treatment of these patients due to the multidrug-resistance patterns of this yeast species. Using VITEK-2 system, this study isolate was initially identified as *Cryptococcus laurentii*.

At present, the accurate identification of *C. auris* should be confirmed using accepted methods such as MALDI-TOF MS or molecular identification techniques. Difficulties in mycological identification of *C. auris* using conventional phenotypic systems and the limited access to MALDI-TOF MS and molecular biology tools in routine laboratories may contribute to the underestimation of this yeast. Also, new CHROMagar media have been developed to identify *C. auris* in routine laboratories[11]. Our isolate exhibited higher minimal inhibitory concentrations for fluconazole which is in concordance with the reports in the literature[12,13]. This report contributes to knowledge of the epidemiology of *C. auris* infections in individuals with an underlying disease. This case is an example of the importance of timely confirmation since conventional laboratory techniques may lead to misidentification and, consequently, inappropriate management.

Table 1. Minimal inhibitory concentrations (µg/ml) of various antifungal agents against *C. auris*

	MFG	CAS	AMB	5FC	FLC	ITC	VRC	PCZ	AFG
Candida auris	0.25	>8	2	0.25	>256	>16	>8	>8	0.25

MFG: Micafungin, CAS: Caspofungin, AMB: Amphotericin B, 5FC: Flucytosine, FLC: Fluconazole, ITC: Itraconazole, VRC: Voriconazole, PCZ: Posaconazole, AFG: Anidulafungin

Conclusion

C. auris is an emerging and opportunistic multidrug-resistant human pathogen. It is necessary to strengthen measures to achieve not only accurate and quick identification, but also to avoid its dissemination by improving the infection control measures and promoting antifungal stewardship in healthcare facilities.

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Ethics

Informed Consent: Informed consent could not be obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.G.M., Concept: L.T., E.S.A., Design: L.T., Data Collection or Processing: L.T., E.S.A., D.G.M., Analysis or Interpretation: L.T., E.S.A., Literature Search: L.T., Writing: L.T., E.S.A.

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