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Prompt Diagnosis and Effective Treatment of *Trichosporon asahii* Catheter-Related Infection in Non-immunocompromised Neurosurgical Patient

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Abstract *Trichosporon asahii* is a rare but emerging fungal pathogen that causes severe and life-threatening infections with high mortality rate, mostly in immunocompromised patients. It could be easily misdiagnosed due to lack of awareness, especially when invasive or deep-seated infections occur in non-immunocompromised patients, and inadequately treated since the clinical failures and high minimum inhibitory concentrations to some antifungal agents have been described. We present a case of *T. asahii* catheter-related infection in 66-year-old comatose patient with polytrauma, who was not immunodeficient, but was receiving broad-spectrum antibiotics for a long period. Due to prompt diagnosis and treatment which included catheter replacement and voriconazole, the patient successfully recovered from this infection. The aims of this case report were to highlight the importance of recognizing this otherwise colonizing yeast as potentially dangerous pathogen in non-immunocompromised patients with a long-term antibiotic therapy, and to emphasize the importance of the right therapeutic choice due to its resistance to certain antifungal agents.

Keywords *Trichosporon* · Catheter-related infection · Non-immunocompromised patient · Voriconazole

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Introduction

Trichosporon species are yeasts that belong to Sporidiobolaceae family of Basidiomycota phylum. Members of the genus may be found in the external environment, but also as a part of normal flora of the human skin, respiratory, and gastrointestinal tract [1]. All pathogenic members of the genus *Trichosporon* were once regarded as a single species, *Trichosporon beigelii*, but today, they are divided into distinct species, among which *Trichosporon asahii* is the most common cause of disseminated disease [2]. The specific medical conditions like neutropenia, malignancy, burns, corticosteroid therapy, organ transplantation, or low birth weight

in infants could underlie the life-threatening *Trichosporon* infection [3–6]. The cases of deep-seated or invasive *Trichosporon* infections in non-immunocompromised patients are rare. In this report, we present a case of *T. asahii* catheter-related infection in a comatose patient who was not immunodeficient, but was receiving broad-spectrum antibiotics for a long period. We emphasize the possibility of such infections in non-immunocompromised patients with a long-term antibiotic therapy, and the importance of the adequate treatment due to its resistance to certain antifungal agents. We also provide a brief review of other possible aggravating factors described in rare cases of trichosporonosis in non-immunocompromised patients.

Case Report

A 66-year-old man was admitted to the intensive care unit (ICU) because of polytrauma sustained due to a fall from a tree. On admission, he was comatose with Glasgow Coma Score (GCS) 7/8 and had spontaneous but insufficient breathing. The blood pressure was 100/50 mmHg at first and 80/50 mmHg at second reading. Pulse was 90/min. Laboratory tests were normal, including hemoglobin, hematocrit, white blood cell count (7,100/μL), and blood chemistry tests with an exception of elevated glucose level (185.4 mg/dL).

The patient was intubated and anesthetized. A chest drain was inserted in the right pleural space. Intravenous prophylactic therapy with ciprofloxacin and metronidazole was initiated. Crystalloids infusion, gastroprotection, analgesics, diuretics, and anti-tetanus prophylaxis were also included in therapy.

Multislice computed tomography (MSCT) of head, cervical spine, chest, and abdomen showed multiple fractures of skull vault and base, epidural and subdural hemorrhages, dura mater lesion, brain concussion, sternal fracture, pneumocephalus, laminar fracture of C6 vertebrae, fractures of the 7th and 8th left ribs, and bilateral hemothorax.

The patient was surgically treated twice. On the day of admission, osteoplastic craniotomy and evacuation of subdural and epidural hematoma were performed. On the sixth day of hospitalization, blood culture was positive for methicillin resistant *Staphylococcus epidermidis* (MRSE) and intravenous linezolid 600 mg twice daily (bid) was included. On the 12th day of hospitalization, bronchial aspirate was positive for *Pseudomonas aeruginosa*, multiresistant *Acinetobacter baumannii*, and extended spectrum beta-lactamase (ESBL)-producing *Proteus mirabilis*; so he was treated intravenously with meropenem 500 mg three-times daily (tid) and colistin 1 million international units (IU) bid.

On the 19th day, he was transferred to neurological intensive care unit (NICU) in coma vigil state. During further period, *P. aeruginosa*, *A. baumannii*, and different ESBL-producing enteric bacteria were repeatedly isolated from blood cultures, bronchial aspirates, and wound swabs. The patient was treated with meropenem, colistin (see above) and gentamicin (80 mg bid, intravenously).

On the day of second surgery, he was receiving colistin and gentamicin for 6 days. He was afebrile and in stable condition.

The second surgery was on the 44th day of hospitalization, when a ventriculoperitoneal shunt was implanted due to development of posttraumatic hypertensive hydrocephalus. A central venous catheter was also inserted, but removed 2 days later because of fever. Blood test showed markedly elevated C-reactive protein (CRP) level (198.3 mg/L) and normal white blood cell (WBC) count (9,080/μL), which increased the next day (11,630/μL).

The removed catheter tip culture was obtained in microbiological laboratory by semiquantitative (Maki's) and quantitative (Cleri's) methods [7]. Both methods showed yeast in significant number of colonies, suggesting the possibility of catheter-related infection. Colony characteristics on blood agar (Bio-Rad, France), and Sabouraud dextrose agar (Bio-Rad, France), microscopic appearance of arthroconidia, negative germ tube test and positive urease test indicated *Trichosporon* species.

Definitive identification of *T. asahii* was achieved by Vitek2 System (bioMérieux, France) and confirmed in National Referral Center for Systemic Mycoses. Although two sets of blood cultures of the patient were negative, using the BacT/ALERT 3D blood culture system (bioMérieux SA, Marcy L'Etoile, France), due to significant number of colonies on catheter tip culture and the presence of general signs of infection, voriconazole was included in therapy 4 days after the removal of the catheter. It was administrated as an intravenous infusion, with a loading dose of 6 mg/kg (600 mg) on first day, and maintenance dose of 4 mg/kg (400 mg) bid. On the fifth day of therapy, the patient became afebrile,

and the inflammation parameters showed decreased levels (CRP 173.5 mg/L; WBC 8,090/μL). On the eighth day of therapy, in consultation with the infectious disease specialist, voriconazole was excluded. CRP continued to decrease. Four days after treatment, it was 77.7 mg/L. During the following period, microbiological findings were normal and the patient has become a candidate for a rehabilitation facility.

Discussion

Invasive and deep-seated trichosporonosis have been recognized as an emerging infection in immunocompromised hosts. *T. asahii* of cutaneous origin may be one of the principal ways through which sporadic invasive or deep-seated trichosporonosis is acquired, and the catheter is the expected route of transmission [6, 8]. The ability to form a biofilm makes this pathogen difficult to treat [9, 10], and affinity for indwelling medical devices predisposes the appearance of blood infection, which sometimes cannot be promptly confirmed in blood cultures. For example, candidemia studies showed that about 50 % of patients with invasive candidiasis are not diagnosed by blood cultures (so-called missing 50 %), with the possible reasons of the absence of viable blastoconidia within the circulation, concentrations that are insufficient to be detected within a collected sample, or intermittent or transient release of viable cells into the bloodstream [11]. The early diagnosis of trichosporonosis is important, but still remains a great challenge; therefore, in the absence of other non-culture diagnostic methods, negative blood cultures should not be the criteria for eliminating the possibility of *Trichosporon* infection in patient with the evidence of significant catheter colonization and elevated inflammation parameters. In the presented case, clinical improvement and negative microbiological findings after catheter removal and voriconazole treatment suggested that *T. asahii* was a cause of systemic infection.

The vast majority of *Trichosporon* fungemias or deep-seated infections have been reported in patients with predisposing factors. Rarely, some cases of trichosporonosis in non-immunocompromised patients have been described and, as with this patient, were associated with long-term hospitalization and prolonged treatment with broad-spectrum antibiotics [8, 12, 13]. Diabetes as a possible favorable condition is also noticed [8, 13]. There is a close relationship between the blood glucose level of the patient and clinical outcome [14]. In this case report, the patient had an elevated glucose level without diagnosed diabetes, which can be considered as potentially aggravating factor. Life-threatening trichosporonosis has been described in non-immunocompromised heavy alcohol consumer [13] and patient with secondary hemochromatosis [15], but none of this was present in the patient from this case.

At the time of this case, the therapeutic choice was made based on review of the pertinent English-language literature, by which the new triazoles have been successful for the treatment of invasive or deep-seated trichosporonosis [5, 12, 14, 16–18]. Some *Trichosporon* isolates show relatively high MICs to fluconazole [4, 5, 19, 20]. Therefore, in conditions of the inability to quickly verify MIC, fluconazole has uncertain efficacy in vivo. Trichosporon shows in vitro resistance to echinocandins [12, 14, 21]. In vitro resistance has also been reported to amphotericin B, and low success rates have been accomplished with monotherapy [3, 4, 12, 16]. The awareness of the resistance is important since the increasing use of antifungal drugs in the ICU may lead to the selection and isolation of more resistant species in the future. Therefore, in patients who develop symptoms and signs of unexplained infection while receiving treatment with fluconazole, echinocandins, or amphotericin B, *Trichosporon* infection is one of the possibilities that should be considered.

The possibility of inadequate treatment due to lack of clinical breakpoints for antifungal agents in microbiology laboratory's routine practice should lead to development of clinical breakpoint standards for *Trichosporon* and other rare invasive yeast isolates in the near future. The same reasons have recently led to development of ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections [22].

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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