A case of *Trichosporon asahii* urinary tract infection in a frail elderly patient

Nicola Acampora[1], Alessandro Frizza[1], Fabrizio Brau[1], Riccardo Torelli[2,3], Antonietta Vella[2,3], Elena De Carolis[2,3], Massimo Fantoni[2,4]

[1]Dipartimento di Geriatria, Fondazione Policlinico Universitario A. Gemelli IRCCS; Università Cattolica del Sacro Cuore, Rome, Italy;
[2]Dipartimento Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;
[3]Istituto di Microbiologia, Università Cattolica del Sacro Cuore, Rome, Italy;
[4]Istituto di Clinica delle Malattie Infettive, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY

Trichosporon urinary tract infection (UTI) is an unusual emerging infection, caused mostly by *Trichosporon asahii*, described especially in hospitalized patients. To date the interpretation and management of Trichosporon positive urinary culture remains a diagnostic and therapeutic dilemma for which there are no precise indications, and the challenge can be even more complicated in comorbid frail elderly patients. Triazoles are known to be the most effective antifungal drugs but can raise concerns about pharmacological interaction. We report a case of *Trichosporon asahii* nosocomial UTI in an elderly patient.

Keywords: *Trichosporon asahii*, nosocomial opportunistic infection, urinary tract infection, elderly.

INTRODUCTION

Trichosporon species are basidiomycetous yeasts ubiquitous in nature, also as a component of the normal microbiota of the skin, respiratory tract and gastrointestinal tract. This agent can cause superficial infections and opportunistic invasive infections [1, 2]. Invasive trichosporonosis is an increasingly recognized life-threatening illness, occurring mainly in critically ill or immunocompromised hosts, above all with hematologic malignancies [2]. *Trichosporon* urinary tract infection (UTI) is an unusual invasive infection, described especially in hospitalized patients [3, 4]. *Trichosporon asahii* is the most frequent pathogen causing invasive trichosporonosis including UTI [4, 5]. Detection of *Trichosporon asahii* in urine culture specimen in hospitalized patients represents a clinical challenge because of the lack of well-defined and specific indications for the clinical interpretation and treatment [2]. This challenge can be even more complicated in frail elderly patients who usually have comorbidities and polypharmacy.
We report a case of *Trichosporon asahii* UTI in a frail, comorbid, elderly patient in a tertiary care setting.

Corresponding author
Massimo Fantoni
E-mail: massimo.fantoni@policlinicogemelli.it

CASE REPORT

An 80-year-old male diabetic patient was admitted to our hospital because of confusion and gross hematuria. His medical history included advanced Alzheimer's dementia, ischemic cardiomyopathy with history of by-pass surgery and benign prostatic hypertrophy. His medication

included insulin glargine, insulin aspart, clopidogrel, simvastatin, nitroglycerin, amlodipine, omeprazole and promazine. He was completely dependent from care-giver in activities of daily living and he was frail according to Fried criteria. One week before admission, he had developed dysuria and gross hematuria. Ciprofloxacin was started but hematuria and progressive confusion persisted, and he was referred to the emergency department of our hospital.

On arrival, a urinary catheter was introduced, with the evidence of hematuria in the catheter bag. Laboratory test revealed creatinine 1.86 mg/dL, urea nitrogen 37 mg/dL, reactive C protein 126.6 mg/L, normal leucocyte count. Urinalysis revealed presence of hemoglobin and red cells. A cystoscopy was performed with the evidence of adenomatous adherent residues coated with easily bleeding mucosa and absence of neoplastic lesions. On second day, afebrile chills developed, a urinary specimen was sent for culture (turned out to be negative), intravenous ampicillin was started, and he was admitted to the Geriatrics Department. On examination he was lethargic, had normal vital signs and tenderness on palpation in hypogastric area. Hematuria was still present in the catheter bag. Laboratory tests showed a further increase in C-reactive protein. On third day of stay the temperature rose to 38°C. Because of poor clinical response to antibiotic therapy, ampicillin was discontinued, and a new urine specimen was sent for culture while intravenous meropenem and teicoplanin were started. The results of urine culture showed the growth of a yeast on Candida BCG (brom cresol green) agar plates (Meus-Italy) that was identified to be *Trichosporon asahii* using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Figure 1).

A second culture performed after catheter replacement and interruption of antibiotic therapy confirmed the growth of the yeast. Antifungal susceptibility test, performed with Sensititre™ YeastOne YO10 (Thermo Scientific), revealed voriconazole susceptibility. Voriconazole was started with clinical improvement. Because voriconazole may reduce the efficacy of clopidogrel by inhibition of CYP2C19, given the history of ischemic heart disease with bypass, clopidogrel was replaced with low-dose aspirin. The patient was discharged from the hospital to a nursing home setting, remained afebrile and a urine culture performed one week after discontinuation of voriconazole was negative for *Trichosporon* species.

Figure 1 - *Trichosporon asahii* colonies on Candida BCG agar plate.

DISCUSSION

Trichisporon species are found ubiquitously in the environment, mainly in soil but also on surfaces of hospital wards. The yeast could be a normal component of physiological microbiota of the skin, particularly peri-genital skin, and could occasionally colonize gastro-intestinal or respiratory tract and vagina. Occasionally it can cause superficial infection, such as white piedra, and even systemic life-threatening infection, known as invasive trichosporonosis [1, 2]. Colonization of mucosal or cutaneous surfaces is probably the first step in the pathophysiology of systemic infections, because of a break in the integrity of the barrier and subsequently spread to bloodstream.

Invasive trichosporonosis has been increasingly recognized, above all in seriously immunocompromised patients, like those with hematologic malignancies and neutropenia, in which *Trichosporon* fungemia became the second most common cause of disseminated yeast infections after *Candida* infection [6]. Hosts of invasive trichosporonosis are also critically ill patients, admitted to intensive care units where they undergo invasive procedures and broad-spectrum antibiotic therapies [5, 7]. Recently, *Trichosporon* inva-

sive infection is increasingly recognized even in patients without severe immunologic deficiency or critically life-threatening disease, suggesting the need to consider some immunocompetent subjects at risk of infection, such as comorbid frail older people in which many risk factors are added together, like our patient [4].

Trichosporon asahii infections are more common in patients with alterations of innate immune response, such as chemotherapy-induced neutropenia [8]. The changes that occur in an older adult's immune system are very complex; this phenomenon is called "immunosenescence" and involves virtually all immune cell lineages [9]. Age-associated changes in neutrophils include both impaired responses and inappropriate persistence of inflammation that may result from alterations in signal transduction. Neutrophils from older adults show diminished signalling via the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor that usually mediates antiapoptotic cell survival [10]. Also in patients affected by diabetes mellitus, like our patient, neutrophilic dysfunction is often present which is a well known predisposing factor for bacterial and fungal opportunistic infections [11]. In addition, poor peripheral circulation, often present in this group of patients, leads to diminished delivery of neutrophils to sites of microbial entry and this is even worsened if chronic heart failure is present. All of these factors may contribute, in a non-immunocompromised older adult, to develop an invasive infection by *Trichosporon asahii*.

Virulence traits in *Trichosporon* species are still little known. *Trichosporon asahii* cells can rapidly adhere on devices such as bladder catheters and are able to form biofilms that make them less susceptible to antifungal therapy [12]. Because of this ability, interpretation of the growth of *Trichosporon asahii* in urine culture is difficult in patients with bladder catheter and treated with several antibiotic therapies in which the yeast can easily become a urinary contaminant. To date, the interpretation of the positivity of urine culture remains a diagnostic and therapeutic dilemma for which precise indications do not exist [2]. However, we should be aware that the positivity of urine culture could be the first step of a disseminated infection, even more if bladder mucous membrane is damaged, like in our patient with persistent hematuria [1]. In our case of a diabetic frail old patient, the rise of body temperature during antibiotic therapy, the persistence of inflammatory syndrome and hypogastric tenderness and two positive urine cultures (the second after replacing the bladder catheter), led us to consider *Trichosporon asahii* as the etiologic agent of UTI and not a simple colonizer.

Treviño et al., in their report have isolated *Trichosporon asahii* from 32 hospitalized patients in 2 years of study [13]. Median age was of 81 and all of them had urinary catheterization, were under antibiotic therapy, and had severe comorbidities. The authors excluded an infection outbreak by identifying different genotypes of the yeast and concluded that "*T. asahii is, likely, an emergent pathogen in elderly patients with urinary drainage devices*". In their study, susceptibility tests have revealed that this infection *"can be adequately treated with triazoles, with voriconazole being the most active"*. This indication has been recently confirmed by J.N. de Almeida Júnior and C. Hennequin in their systematic review of 203 cases of invasive *Trichosporon* infection from 1994 to 2015. The Authors noticed that "*Voriconazole-based treatment was associated with favorable outcome"*, and "*voriconazole has the best in vitro efficacy against clinical isolates of Trichosporon spp."* [14]. The European Society for Clinical Microbiology and Infectious Diseases, in 2014 clinical guidelines for the diagnosis and management of rare invasive yeast infections, supports the use of triazoles, particularly voriconazole, for treatment of invasive infection caused from *Trichosporon asahii*, that is often *in vitro* resistant to amphotericin B and almost always to echinocandins [15].

Because of the concern about voriconazole drug interaction we preferred to wait for antifungal susceptibility test results rather than start an empirical therapy. However, also in our case *Trichosporon asahii* was resistant to different antifungal classes and had a good susceptibility to voriconazole. With voriconazole, the clinical condition of the patient improved, and a urine culture performed after a week was negative for *Trichosporon asahii*.

In conclusion, our case confirms that UTI by *Trichosporon* is an emerging problem in hospitalized patients, even without severe immunological impairment. In elderly patients, frailty, comorbidity and polypharmacy may cause problems in interpretation, treatment choice and outcome.

Voriconazole has proved effective also in our case against *Trichosporon asahii*, but has raised some concerns about drug interactions, that have to be considered particularly in elderly patients.

Conflicts of interest: All authors have none to declare.

REFERENCES

[1] Haupt H.M., Merz W.G., Beschorner W.E., et al. Colonization and infection with *Trichosporon* species in the immunosuppressed host. *J. Infect. Dis*. 147, 199-203, 1983.
[2] Colombo A.L., Padovan A.C., Chaves G.M. Current knowledge of *Trichosporon* spp. and trichosporonosis. *Clin. Microbiol. Rev*. 24, 682-700, 2011.
[3] Febre N., Silva V., Medeiros E.A., et al. Microbiological characteristics of yeasts isolated from urinary tracts of intensive care unit patients undergoing urinary catheterization. *J. Clin. Microbiol*. 37, 1584-1586, 1999.
[4] Khan I.D., Sahni A.K., Basu A., Haleem S. *Trichosporon asahii* urinary tract infection in immunocompetent patients. *Med. J. Armed Forces India* 71, 373-376, 2014.
[5] Ruan, S.Y., Chien J.Y., Hsueh P.R. Invasive trichosporonosis caused by *Trichosporon asahii* and other unusual Trichosporon species at a medical center in Taiwan. *Clin. Infect. Dis*. 49, 11-17, 2009.
[6] Pagano L., Caira M., Candoni A., et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 91, 1068-1075, 2006.
[7] Wolf D.G., Falk R., Hacham M., et al. Multidrug-resistant *Trichosporon asahii* infection of nongranulocytopenic patients in three intensive care units. *J. Clin. Microbiol*. 39, 4420-4425, 2001.
[8] Suzuki K., Nakase K., Kyo T., et al. Fatal *Trichosporon* fungemia in patients with hematologic malignancies. *Eur. J. Haematol*. 84, 441-447, 2010.
[9] Salvioli S., Monti D., Lanzarini C., et al. Immune system, cell senescence, aging and longevity-inflamm-aging reappraised. *Curr. Pharm. Des*. 19, 1675-1679, 2013.
[10] Shaw A.C., Goldstein D.R., Montgomery R.R. Age-dependent dysregulation of innate immunity. *Nat. Rev. Immunol*. 13, 875-887, 2013.
[11] Rammaert B., Lanternier F., Poirée S., Kania R., Lortholary O. Diabetes and mucormycosis: a complex interplay. *Diabetes Metab*. 38, 193-204, 2012.
[12] Di Bonaventura G., Pompilio A., Picciani C., et al. Biofilm formation by the emerging fungal pathogen *Trichosporon asahii*: development, architecture, and antifungal resistance. *Antimicrob. Agents Chemother*. 50, 3269-3276, 2006.
[13] Treviño M., García-Riestra C., Areses P., et al. Emerging *Trichosporon asahii* in elderly patients: epidemiological and molecular analysis by the Diversi-Lab system. *Eur. J. Clin Microbiol. Infect. Dis*. 33, 1497-1503, 2014.
[14] De Almeida Júnior J.N., Hennequin C. Invasive *Trichosporon* infection: a systematic review on a re-emerging fungal pathogen. *Front. Microbiol*. 7, 1629, 2016.
[15] Arendrup M.C., Boekhout T., Akova M., et al. ESCMID/ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin. Microbiol. Infect.* 20, Suppl. 3, 76-98, 2014.