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Note

Possible *Trichosporon asahii* urinary tract infection in a critically ill COVID-19 patient

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ABSTRACT

Background: *Trichosporon asahii*, an emerging fungal pathogen, has been frequently associated with invasive infections in critically ill patients.
Case report: A 74-year-old male patient diagnosed with COVID-19 was admitted to an Intensive Care Unit (ICU). During hospitalization, the patient displayed episodes of bacteremia by *Staphylococcus haemolyticus* and a possible urinary tract infection by *T. asahii*. While the bacterial infection was successfully treated using broad-spectrum antibiotics, the fungal infection in the urinary tract was unsuccessfully treated with anidulafungin and persisted until the patient died.
Conclusions: With the evolving COVID-19 pandemic, invasive fungal infections have been increasingly reported, mainly after taking immunosuppressant drugs associated with long-term broad-spectrum antibiotic therapy. Although *Candida* and *Aspergillus* are still the most prevalent invasive fungi, *T. asahii* and other agents have emerged in critically ill patients. Therefore, a proper surveillance and diagnosing any fungal infection are paramount, particularly in COVID-19 immunocompromised populations.

Posible infección del tracto urinario por *Trichosporon asahii* en un paciente crítico con COVID-19

Palabras clave:
COVID-19
SARS-CoV-2
Resistencia a los antimicóticos
Hongos emergentes
Trichosporon asahii
Infección del tracto urinario

RESUMEN

Antecedentes: *Trichosporon asahii*, un hongo patógeno emergente, se ha asociado con frecuencia con infecciones invasivas en pacientes enfermos en estado crítico.
Caso clínico: Un paciente de sexo masculino de 74 años de edad, con diagnóstico positivo para la COVID-19, ingresó en una unidad de cuidados intensivos. Durante la hospitalización el paciente presentó episodios de bacteriemia por *Staphylococcus haemolyticus* y una posible infección del tracto urinario por *T. asahii*. Mientras la infección bacteriana fue tratada exitosamente con antibióticos de amplio espectro, la infección micótica urinaria no remitió con anidulafungina y persistió hasta la muerte del paciente.
Conclusiones: Con la pandemia de la COVID-19 se han notificado cada vez más casos de infecciones micóticas invasivas, principalmente después del uso de fármacos inmunosupresores, asociados con terapia de antibióticos de amplio espectro. Aunque *Candida* y *Aspergillus* siguen siendo los hongos invasores más prevalentes, *T. asahii* y otras especies han emergido en pacientes enfermos en estado crítico. Por lo tanto, la vigilancia y el diagnóstico de las infecciones micóticas es primordial, particularmente en poblaciones inmunodeficientes por la COVID-19.

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The COVID-19 pandemic has caused millions of deaths worldwide. It has been reported that patients with comorbidities, coinfections, and secondary infections have the worst prognosis.[8,9] Noteworthy, *Trichosporon asahii*, an emerging pathogen associated with invasive infections in critically ill patients, has been an etiological agent of coinfection and fungemia in COVID-19 patients.[1,2] In the present case study, bacteremia by *Staphylococcus haemolyticus* and a possible urinary tract infection (UTI) by *T. asahii* in a critically ill patient with COVID-19 is reported.

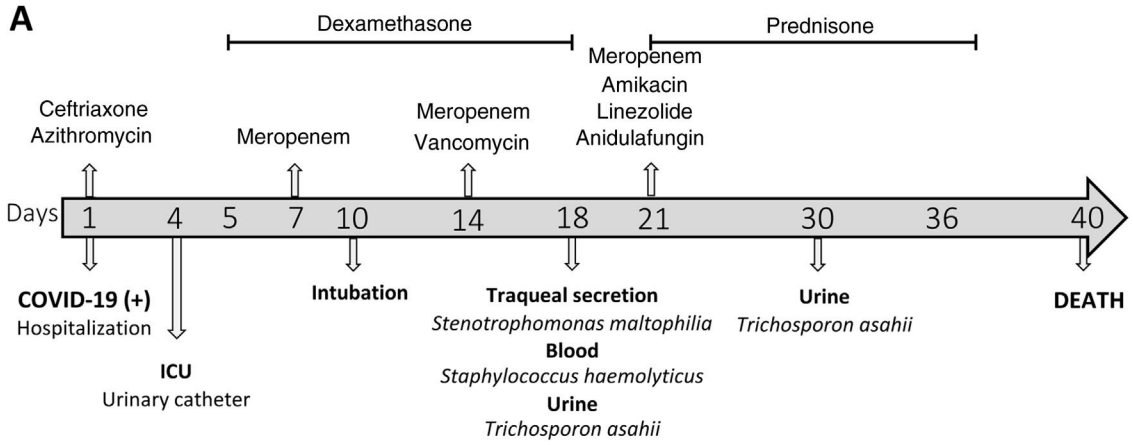
In January 2021, a 74-year-old male patient with a history of hypertension and type II diabetes was admitted to a Brazilian hospital with laboratory-confirmed SARS-CoV-2. For six days, the patient was experiencing diarrhea without mucus and blood (~6 episodes/day), sporadic unproductive cough, asthenia, and unmeasured fever. Upon hospital admission, empirical antibacterial therapy with ceftriaxone (1 g/24 h, IV) and azithromycin (500 mg/24 h, PO) was administered (Fig. 1A).

After three days, the patient presented hyponatremia (Na = 126 mEq/L), abnormal results of kidney function (114 mg/dL urea, 2.5 mg/dL creatinine), anemia (11.7 g/dL hemoglobin), increased lactate dehydrogenase activity (366 U/L) and higher concentration of C-reactive protein (PCR, 53 mg/L), with normal leukocyte counts. Moreover, the urinalysis revealed the presence of hemoglobin and protein. The observed hematuria, proteinuria and renal insufficiency pointed to a nephritic syndrome. The patient was fitted with an indwelling urinary catheter and transferred to the COVID-19 intensive care unit (ICU).

On day 5, corticosteroid therapy with dexamethasone (6–10 mg/24 h) was started. This treatment lasted for eight days and was then switched to prednisone (40 mg/24 h) for 15 days. On day 7, antibiotic therapy was changed to meropenem (1 g/12 h, IV) and, after 7 days, vancomycin (1 g/48 h, IV) was added. On day 10, the patient underwent endotracheal intubation and mechanical ventilation (Fig. 1A).

Blood, tracheal secretion, and urine cultures were performed with samples collected 15 days after ICU admission (Fig. 1A). Bacterial and fungal species were identified using Vitek® 2 Compact (bioMérieux, São Paulo, Brazil) and confirmed by MALDI-TOF (Biotyper®, Bruker, Massachusetts, USA). *S. haemolyticus* was isolated from blood and exhibited clindamycin, erythromycin, gentamicin, levofloxacin, oxacillin, and rifampicin resistance; *Stenotrophomonas maltophilia*, susceptible to trimethoprim/sulfamethoxazole, was isolated from the tracheal secretion (>100,000 CFU/mL). Interestingly, *T. asahii* (>100,000 CFU/mL) was isolated on cystine lactose electrolyte deficient (CLED) agar from the urine sample. Despite the fungal presence, the patient did not exhibit any symptom related to an urinary tract infection. *T. asahii* isolate (which was assigned the reference HGN1) was subcultured on Sabouraud dextrose agar, and images of the colony and microscopic structures were captured (Fig. 1B).

On day 21, the patient was administered erythropoietin (4000 UI, 3×/week) and a combined antimicrobial therapy comprised of meropenem (1 g/12 h, IV), amikacin (500 mg/24 h, IV), linezolid (600 mg/12 h, IV), and anidulafungin (100 mg/12 h, IV) (Fig. 1A). On day 29, a RT-PCR test showed the persistence of SARS-CoV-2 infection. Although new tracheal secretion and blood cultures were negative, *T. asahii* (>100,000 CFU/mL) was still detected in the urine culture, which was associated with an increased number of leukocytes (>50 cells per field) and red blood cells (>30 cells per field) in the urine sediment. At that point the patient still had the indwelling urinary catheter, and there were no reports of replacement in the medical record. The patient died 40



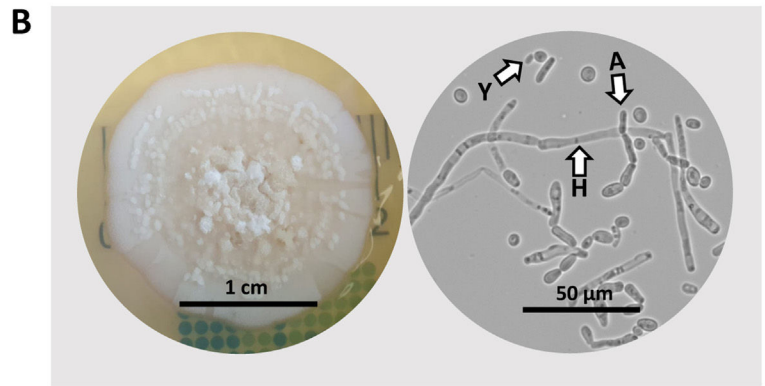


Fig. 1. Clinical course and mycological data of a critically ill COVID-19 patient with a possible urinary tract infection caused by *Trichosporon asahii*. A: Timeline of the clinical evolution of the patient. B: Colony and microscopy of *T. asahii* culture on Sabouraud dextrose agar at 35 °C for three days (Y: yeast, H: hyphae, and A: arthroconidia).

days after hospital admission due to cardiac arrest and acute respiratory distress syndrome, being still SARS-CoV-2 positive (Fig. 1A).

The antifungal susceptibility testing performed using the EUCAST broth microdilution methodology (www.eucast.org) revealed that the *T. asahii* HGN1 strain was susceptible to amphotericin B (AMB, MIC = 2 μg/mL) and all tested azoles. The MICs obtained for fluconazole, voriconazole, itraconazole, posaconazole, and isavuconazole ranged between 0.03 and 1 μg/mL. On the other hand, the MIC value of anidulafungin was quite high (>16 μg/mL). It is well-known that AMB and echinocandins display poor *in vitro* activity against *Trichosporon* and echinocandins do not achieve therapeutic concentrations in the urine.[4,5] It should also be pointed out that, among triazoles, the lowest MIC value in our study was that from voriconazole, considered the best choice to treat *T. asahii* infections.[5] *T. asahii* strain HGN1 was a medium biofilm former, a characterization made with the crystal violet staining method.[7] Indeed, biofilm formation on medical devices, such as urinary catheters, is a cause of persistent infection, often associated with reduced antifungal susceptibility and increased virulence.[3,7] Thus, it is likely that inadequate antifungal treatment with anidulafungin and the indwelling urinary catheter contributed to the observed *T. asahii* persistence in the urine.

In summary, we report a case of a possible UTI caused by the emerging and highly resistant pathogen *T. asahii* in a critically ill COVID-19 patient. Fungal infections have been increasingly reported during the evolving COVID-19 pandemic. Many cases have been associated with immunosuppressant drugs that treat immunological storms, as well as with long-term broad-spectrum antibiotic therapy and invasive medical devices. Thus, this study shows that while *Candida* and *Aspergillus* are still the most prevalent invasive fungi,[10] *T. asahii* and other agents are becoming more prevalent in critically ill patients.[1,2,6] In this sense, surveillance and diagnosis are essential in preventing and treating fungal infections, especially in immunocompromised populations.

Ethical approval

All data were gathered as part of routine work at the Hospital de Guarnição de Natal (Rio Grande do Norte State, Brazil). The Hospital de Guarnição de Natal ethical committee approved this study protocol (N27/2021).

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Conflict of interest

None declared.

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