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Invasive Fungal Infection by *Trichosporon asahii* in Patients with Severe Covid-19: A Five Case Series

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Abstract

Corticosteroids have shown a clear benefit in reducing mortality for patients with severe COVID19, nonetheless, secondary infections have been reported with their use. In this paper, we present five cases of Colombian patients who developed invasive fungal infections by *Trichosporon asahii*. The patients had COVID-19 pneumonia, they were treated with corticosteroids and exposed to broad-spectrum antibiotics. The organism's identification was achieved by MALDI-TOF, microscopy and culture. The patients were treated with itraconazole and amphotericin B deoxycholate. Four out of five patients died.

Keywords: *Trichosporon asahii; Covid-19; SARS-CoV-2; Opportunistic Infections*

Introduction

COVID-19 is a new infectious disease caused by the SARS-CoV-2 virus, which has caused a global health problem. The clinical manifestations of the disease include fever, throat pain, fatigue, cough and dyspnea. Most patients develop a mild to moderate disease, however, around 5 - 10% of patients will develop severe pneumonia which can require invasive mechanical ventilation and even cause death [1]. Currently, the treatment is based on symptom management, fluid administration and maintenance of oxygenation, however, there are various clinical trials that are trying to identify the medication or the combination of these that can effectively treat the disease [2,3].

Corticosteroids are the only therapeutic agents that have shown a clear benefit in reducing mortality for patients with severe Covid-19 [4], however, previous studies have described that patients with viral pneumonia treated with corticosteroids take longer to achieve viral clearance and may show adverse reactions such as psicosis, hyperglycemia, avascular necrosis and a higher number of secondary infections [5].

In relation to infections, COVID-19 patients have higher rates of bacterial superinfection compared to influenza patients [6], thus they are exposed to high doses of broad spectrum antibiotics. Apart from this, the development of mycotic opportunistic infections such as pulmonary aspergillosis, oral candidiasis, *Pneumocystis spp* pneumonia [7], mucormycosis [8] and cryptococcosis [9]) has been documented. Recently, cases of pneumonia [10] and fungemia [11] caused by *Trichosporon asahii* on patients with COVID-19 pneumonia have been described.

Trichosporon asahii is a ubiquitous yeast in nature, it is present on the ground, water, plants, mammals, birds and it's part of the human microbiome, nevertheless, sometimes it can be pathogenic. Trichosporonosis has been associated with superficial skin and hair infections, hypersensitivity pneumonitis, chronic pneumonia, meningitis, endocarditis, disseminated infections and fungemia. Risk factors for this infection include neutropenia, organ transplant, diabetes, end stage kidney disease, HIV infection, invasive medical devices and the use of immunosuppressive agents [12].

In this study, we report five cases of Colombian patients with Covid-19 pneumonia treated with corticosteroids and exposed to broad spectrum antibiotics, who developed invasive fungal infection by *Trichosporon asahii.*

Case 1

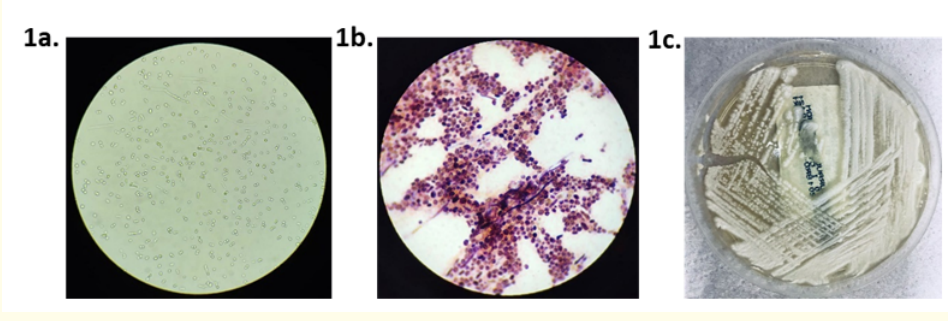
A 69-year-old male patient without any important medical conditions comes to the hospital with respiratory symptoms compatible with Covid-19 confirmed by PCR. The patient was not yet vaccinated. The day of admission he was empirically treated for community acquired pneumonia (CAP) with ceftriaxone (1 gram every 12 hours IV), clarithromycin (500 mg every 12 hours IV) and dexamethasone (6 mg every 24 hours IV). He is immediately admitted to the intensive care unit (ICU), put on non-invasive mechanical ventilation (PEEP: 6, FiO_2: 50%), alternating with high flow nasal cannula, 7 days later he required orotracheal intubation (OTI) because of deterioration of his respiratory pattern. 14 days later while on invasive mechanical ventilation the patient presented elevation of acute phase reactants, fever, deterioration of ventilatory parameters (Leukocytes 17.280 103/ml, neutrophils 14.800103/m, TV 640 ml, PEEP 10, RR 30, FiO_2 40%) and he was diagnosed with extended spectrum beta lactamase producing *Klebsiella oxytoca* tracheitis, thus he was treated with meropenem (1 gram every 8 hours IV). The Ostrosky and candida scores were calculated; this last one was higher than 2.5, so empirical treatment with fluconazole (200 mg every 12 hours IV) was initiated. Later on, a urine culture reported *Trichosporon asahii* by MALDI-TOF, so itraconazole (200 mg every 12 hours IV) and Amphotericin B deoxycholate (0.7 mg/kg/day IV) were initiated for 14 days.

At 57 days of hospitalization, he had again elevated acute phase reactants and developed fever (leukocytes 22,67 103/ml, neutrophils 88,2%, CRP: 30 mg/L), with negative blood cultures but positive urine culture for a yeast identified by MALDI-TOF, which confirmed a relapse of *Trichosporon asahii* urinary tract infection. Treatment with Amphotericin B deoxycholate (0.7 mg/kg/day) and voriconazole (6 mg/Kg every 12 hours for 24 hours and then 4 mg/kg/day) was started. At the moment of the first yeast isolation the patient had been on invasive mechanical ventilation for 14 days, 18 days with a central venous catheter and 24 days with a bladder catheterization. He received dexamethasone for 14 days (6 mg/day). The patient died 7 days after the initiation of the second antifungal treatment. The time between his admission and the first isolation of the yeast was 21 days. The time elapsed between the end of the dexamethasone administration cycle and the first yeast isolation was 7 days.

Case 2

71-year-old female patient, history of lupus, hypertension and venous insufficiency. She comes to the hospital with respiratory symptoms compatible with Covid-19, later confirmed by PCR. The patient had not yet received vaccination. The day of admission she was started on empirical CAP treatment with ceftriaxone (1 gram every 12 hours IV), clarithromycin (500 mg every 12 hours IV) and Covid-19 treatment with dexamethasone (6 mg every 24 hours IV) for 10 days. After 24 hours, the patient was admitted to the ICU and was immediately intubated due to deterioration of her respiratory pattern and bad oxygenation with the following parameters: TV: 360 mL, PEEP

10, RR 18, FiO_2 100%. After 16 days on invasive mechanical ventilation the patient had an increase of acute phase reactants, developed a fever and deterioration of her ventilation parameters (Leukocytes 10.270, TV 450 RR 30, PEEP 16, FIO_2 100%) and was diagnosed with multisensitive *Klebsiella pneumoniae* tracheitis, she persisted febrile event though she was receiving meropenem (1 gram every 8 hours since 5 days ago). The Ostrosky and candida scores were calculated with positive results for empirical coverage of fungal forms; she was started on Voriconazole (200 mg every 12 hours IV) and amphotericin B deoxycholate (0.7 mg/kg/day). The patient died without reaching the end of the treatment, the urine sample analyzed with MALDI-TOF confirmed urinary tract infection by *Trichosporon asahii* (Pictures 1a-1c).



Picture 1a-1c: *1a. Microscopical picture of the fungal forms compatible with Trichosporon spp in a fresh urine sample. 1b Microscopic view of a gram stain from a urine sample showing fungal forms compatible with Trichosporon spp. 1c. Agar Sabouraud culture with the growth of colonies compatible with Trichosporon asahii. Source: Archive from the Latin American team for the investigation of infectious diseases and public health (ELISAP).*

At the moment of this fungal isolation, the patient had been 17 days on invasive mechanical ventilation, 17 days with a central venous catheter and 18 days with a bladder catheter. She was in the ICU for the entire duration of her hospitalization, she received 10 days of dexamethasone (6 mg/day). The patient died 24 hours after the sample was taken and the indication of treatment (couldn't be started). The time between admission and the isolation of the yeast was 16 days. The time between the closure of the dexamethasone cycle and the first yeast isolation was 6 days.

Case 3

A 59-year-old male with no important medical conditions was admitted with a bad general appearance, he was accepted from another hospital, already on orotracheal intubation since 72 hours ago and admitted directly to the ICU. In his medical history there was evidence of respiratory symptoms compatible with Covid-19, confirmed by an antigen test. The patient was not yet vaccinated. On the day of his admission, he was started on empirical CAP treatment with ceftriaxone (1 gram every 12 hours IV), clarithromycin (500 mg every 24 hours IV), and Covid-19 treatment with dexamethasone (6 mg every 24 hours IV) was indicated. The patient had a report from the other hospital of a tracheal aspiration culture that was positive for *Acinetobacter baumannii* and *Klebsiella oxytoca,* so cefepime (2 grams every 8 hours IV) and Amikacin (1 gram every 24 hours IV for 5 days) were started. He was extubated at 5 days of his admission to the hospital and 7 days later he developed a fever, and his general state was compromised but without the need for inotropes or intubation. Samples of urine and blood were gathered and the Ostrosky and candida scores were calculated with a higher than 2.5 result on the second tool, so empirical treatment with voriconazole (6 mg/kg every 12 hours for 24 hours and then 4 mg/kg/day) and amphotericin B deoxycholate (0.7 mg/kg/day) was started until getting the culture results. The presence of *Trichosporon asahii* was identified on the urine culture by MALDI-TOF, which suggests a urinary tract infection and treatment with voriconazole was continued. The patient was discharged with home medical attention.

At the moment of the fungal isolation, the patient was not on invasive mechanical ventilation, nor did he have any medical devices implanted, he was in the ICU for the entire hospitalization and received 10 days of dexamethasone (6 mg/day). The time between admission and positive COVID-19 PCR and the isolation of the yeast was 15 days. The time elapsed between the closure of the dexamethasone cycle and the isolation of the yeast was 5 days.

Case 4

70-year-old male patient, with a history of endoscopic ureterolithotomy and double J catheter, type 2 Diabetes mellitus, hypertension and chronic kidney disease. He was admitted to the hospital presenting with urinary symptoms and respiratory symptoms compatible with Covid-19 confirmed through PCR. The patient was not vaccinated. The next day he started treatment for CAP with ceftriaxone (1 gram every 12 hours IV), Clarithromycin (500 mg every 12 hours IV) and dexamethasone was indicated for Covid-19 (6 mg every 24 hours IV). He was admitted to the emergency department with a rapid deterioration of his respiratory pattern, with hypoxemia reflected on blood gasses, requiring admission to the ICU where he was later intubated. A tracheal aspirate culture was negative for common aerobes. His leukocytes were 14.810 and neutrophils were 13.800. After 4 days of invasive mechanical ventilation the patient had an elevation of acute phase reactants and deterioration of his ventilation parameters, an increase of leukocytes 20.750 with 17.040 neutrophils was noted, PEEP 12, FiO_2 50% with no germ isolation. Treatment for Hospital acquired pneumonia was started with piperacillin tazobactam (4.5 grams every 6 hours) with empirical treatment for oxacillin resistant gram-positive cocci with vancomycin (1 gram every 12 hours IV). Blood cultures were negative. Urine culture revealed yeasts sent for identification through MALDI-TOF, and they were compatible with *Trichosporon asahii*. The patient died before receiving treatment for urinary tract infection.

At the moment of the yeast isolation, the patient had been on invasive mechanical ventilation for 5 days, 5 days with a central venous catheter and 5 days with a bladder catheter. All of this time he had been in the ICU, he received 5 days of dexamethasone (6 mg/day). The time between admission and the isolation of the yeast was 5 days.

Case 5

A 76-year-old male was admitted to the hospital with respiratory symptoms compatible with Covid-19, confirmed with a PCR test. The patient was not vaccinated. Empirical treatment for CAP was started with ceftriaxone (1 gram every 12 hours IV), clarithromycin (500 mg every 12 hours IV), and he received treatment for Covid-19 with dexamethasone (6 mg every 24 hours IV). He was admitted to the emergency department where he remained for 4 days. His respiratory pattern worsened and required oxygenation with a non-rebreather mask. His blood gasses were pCO_2: 34.4 PO_2: 89.1 pH: 7.39 HCO_3: 20.8 BE: -3.2 SO_2: 96.7% FIO_2: 90% PaFi: 99. He was later taken to the ICU and was put on non-invasive mechanical ventilation.

After 3 days in the ICU, he developed tachypnea and was intubated as a rescue measure (PEEP 12, FIO_2 100%, TV 440, RR 16). At that moment the patient had lowering acute phase reactants compared to the initial values (Leukocytes 17.950 ml, neutrophils 16.680 ml). After 4 days on invasive mechanical ventilation, the patient persisted with leukocytosis and neutrophilia, so a tracheal aspiration was performed, yielding the diagnosis of *Enterobacter cloacae* (SPICEM group), he was then started on Trimethoprim sulfamethoxazole (80+400 mg every 8 hours). After 9 days on antibiotics, a control tracheal aspirate was made, isolating *Stenotrophomonas maltophilia*, continuing Trimethoprim sulfamethoxazole for 14 days. The patient continued to deteriorate, a urinary tract infection was diagnosed, isolating *Trichosporon asahii* by MALDI-TOF. The patient died without the opportunity to receive treatment.

At the moment of the yeast's isolation the patient had been 20 days on mechanical ventilation, 17 days on central venous catheter and 17 days with a bladder catheter.

Discussion

This is the first case series reporting an invasive fungal infection with isolation of *Trichosporon asahii* in urine cultures in Covid-19 patients. At the moment of this report, a case of pneumonia and six cases of fungemia by this pathogen have been described (Table 1). Uri-

nary tract infections by *Trichosporon asahii* haven been underreported in literature [13-15] and there are no cases described in Colombia, nevertheless, the included Covid-19 patients in this study are characterized by prolonged exposure to corticosteroids, antibiotics, medical devices, and a long period of hospitalization, they had all the risk factors for the development of said infection. The difference between infection and colonization is another clinical challenge, in these cases the definition of likely clinical disease by invasive Trichosporonosis was made taking into account the definitions of opportunistic invasive fungal infections (IFI) published in 2008 by the Cooperative group of the European organization for research and treatment of cancer/Invasive fungal infections (EORTC/IFICG) and the National institute of allergies and infectious diseases and mycoses (NIAID/MSG) [16] and was consolidated supported on the review and update of consensuated definitions of IFI of the European organization for research and treatment of cancer, the study group for the investigation of mycoses and the research consort emitted in the year 2019; yielding the criteria for probable fungal infection [17].

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**
Country	Spain	Qatar	Brazil	Brazil	Brazil	Brazil	Brazil
Gender, age	Male, 58	Male, 58	Male 57	Male, 74	Female, 75	Male, 73	Male, 72
Invasive mechanical ventilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Previous use of antibiotics	Azithromycin	Piperacillin tazobactam	Piperacillin tazobactam	Piperacillin tazobactam	Piperacillin tazobactam	Piperacillin tazobactam	Piperacillin tazobactam
Use of corticosteroids	Methylprednisolone, 125 mg/day for three days	Non specified steroids	Methylprednisolone 1 mg/kg/day or prednisolone 40 mg/12 hours	Methylprednisolone 1 mg/kg/day or prednisolone 40 mg/12 hours	Methylprednisolone 1 mg/kg/day or prednisolone 40 mg/12 hours	Methylprednisolone 1 mg/kg/day or prednisolone 40 mg/12 hours	Methylprednisolone 1 mg/kg/day or prednisolone 40 mg/12 hours
Previous of corticosteroids	Hydroxychloroquine sulfate 400 mg, Lopinavir/Ritonavir (400 mg/100 mg), Tocilizumab (two doses 8 mg/kg/IV)	Favipiravir, Tocilizumab (total dose of 1200 mg in two doses)	Echinocandins	Echinocandins	Echinocandins	Echinocandins	Echinocandins
Type of *Trichosporon* infection	Pneumonia	Fungemia	Fungemia	Fungemia	Fungemia	Fungemia	Fungemia
Other infections	*Pseudomonas sp- stenotrophomonas sp*	No	Candidemia	Candidemia, *Enterococcus spp.*	Candidemia	No	*Enterococcus spp.*
Trichosporon Treatment	Voriconazole	Voriconazole	Voriconazole	None	Voriconazole, amphotericin B	Voriconazole, amphotericin B	Voriconazole, amphotericin B
Diagnostic test	MALDIT OF	MALDIT OF	MALDIT OF	MALDIT OF	MALDIT OF	MALDIT OF	MALDIT OF
Outcome	Death	Recovered	Recovered	Recovered	Death	Death	Death
Reference	10	11	16	16	16	16	16

Table 1: *Demographic and clinical characteristics of the patients with reported Trichosporon asahii and covid-19 reported in literature.*

Including this case series, death has been the main outcome in 9 out of 12 cases (75%) reported to date. Previous studies have shown that the rate of mortality of *Trichosporon spp* infection can range from 53% to 80% [18-22]; however, in these studies global mortality is taken into account without establishing a cause relation with the pathogen. A previous investigation that took into account mortality due to *T. asahii* calculated 13.6%, but with important differences according to the type of infection because fungemia was associated with an attributable mortality of 51.5% [12]. The high attributable mortality of this pathogen constitutes a therapeutic challenge.

The main treatment in all the patients included in this study and case reports has been voriconazole alone or in combination with amphotericin B. Before the year 2000, the preferred treatment was amphotericin B, however, this therapy has been reported to be ineffective [23]. Later the combination of amphotericin B with flucytosine was suggested [24]; but there are no studies comparing the combined or individual efficacy with these medications. The guidelines developed by ESCMID/ECMM in 2014 recommend voriconazole for the treatment of trichosporonosis, even though said recommendations seem to be based on *in vitro* results, animal studies and some case reports [25]. In this sense, it is necessary to design clinical trials that evidence the efficacy of the available medications for the treatment of trichosporonosis.

The diagnosis of *T. asahii* infections is always based on the isolation of the organism in a clinical sample. The directed test rarely contributes to the diagnosis because of the difficulty to find the typical structures of the fungus. It's been demonstrated that phenotypic focuses are seldom efficient and direct sequencing of the IGS1 region of the ribosomal DNA is considered the reference method for the identification of *Trichosporon* Species [26,27]; however, MALDITOF mass spectrometry has been shown to be a valuable alternative for routine identification of this organism [28]. In this case series and in other reported studies to date, the diagnosis is made with MALDI-TOF, so it is recommended to use this technology.

Conclusion

Disseminated infection, with positive blood cultures, associated to cutaneous or pulmonary involvement used to be the clinical presentation of trichosporonosis in a select group of immunocompromised patients with malignant neoplasms or transplants; however, recently, this fungus has been recognized as an emergent opportunist that causes invasive infections in high complexity hospitals. In the current pandemic event linked to COVID-19, a selective antibiotic pressure is presented by the routine use of empirical antibiotics, plus, a transitory cellular immunity suppression linked to the mass use of systemic corticosteroids with subsequent dysbacteriosis. These factors can be detonators of the outbreak emergency by this pathogen in hospitals worldwide.

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