

Candida Guilliermondii Meningitis Associated with SARS-Cov-2 Infection: First Case Report

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Abstract

Background: The yeasts of *Candida* genus represent the 4th cause of sepsis. However, they are rarely found in infections of the central nervous system. The diagnosis is difficult and often delayed, worsening the prognosis.

Methods: A 47-year-old patient was admitted at the emergency of the military hospital of Tunis, Tunisia for SARS-COV-2 infection. After 4 days of non-amelioration, a Lumbar Puncture (LP) was performed and culture on Sabouraud with or without Actidione and on ChromAgar® was positive. Biochemical and susceptibility to antifungal drugs tests were performed using Vitek 2 Compact. To confirm this identification, the Internal Transcribed Spacer 1 (ITS 1) gene was amplified and sequenced.

Results: We present here a rare case of *Candida guilliermondii* meningitis in a patient infected by SARS-CoV-2. Although, the isolate was sensible to all antifungal drugs, the patient died with a post-COVID septic shock.

Conclusion: COVID-19 is an important cause of death and the co-infection of the SARS-COV-2 and other killer infections worsens the situation. Our description recommends exploring the risk factors that lead to the development of these neurological manifestations.

Keywords: *Candida* Meningitis; *Candida guilliermondii*; SARS-CoV-2

Introduction

Meningitis is a serious manifestation of the Central Nervous System (CNS). When it is diagnosed, Cryptococcal meningitis was described with the highest frequency, followed by *Candida* meningitis and by *Histoplasma* meningitis [1].

Although candidemia and other forms of invasive candidiasis are common nosocomial infections [2,3], *Candida* infection of CNS is an infrequent manifestation of disseminated infection due to *Candida* species [1,4]. Clinical manifestations of this infection include principally meningitis, diffuse cerebritis with micro abscesses, parenchymal abscesses, and vasculitis [4,5].

Reports of *Candida* neuroinfections include mainly *C. albicans* and *C. parapsilosis* with few reports of *C. krusei*, *C. glabrata*, *C. tropicalis*, *C. dubliniensis* and *C. guilliermondii* [1,5,6].

With the emergence of the novel *Coronavirus*, few articles have reported co-occurring meningitis (Table 1). Up to date, *Candida* Meningitis (CM) among patients with COVID-19 is not yet described.

Risks factors of CM are immunosuppression, previous treatment with antibiotics or corticosteroids, preterm birth, recent abdominal

surgery, neuro-surgery and insertion of invasive derivative systems, intravenous drug use, and intravascular catheters [2]. Despite appropriate treatment, prognosis of CM is poor [1].

Herein, we present a case of *Candida guilliermondii* meningitis in post SARS-CoV-2 positive patient.

Clinical History

A 47-year-old patient with a history of cerebral thrombophlebitis one month ago was admitted at the emergency for a continuous fever (>38.5°C), vomiting, asthenia, myalgia and dyspnea. PCR of the nasopharyngeal swab was positive for SARS-CoV-2. She was hospitalized for 3 days and then was discharged due to the improvement in her condition. Three days later, his neurological condition worsened, necessitating his hospitalization in intensive care (Day 0). The thoraco-abdomino-pelvic CT scan showed an image of condensation of 15 mm in the right postero-basal lung and in the abdominal area of multiple hypodense stalls in the liver suggesting hepatic abscesses. Laboratory tests showed blood glucose at 6.1 mmol/L, Hb at 10.5g/dl, White blood Cell count at $23.85 \times 10^9/L$ with a predominance of neutrophils, C-reactive protein at 190 mg/L, pro-calcitonin at 83 ng/mL, progressively worsening renal failure

with hyperkalaemia and hepatic cytolysis. She was treated with broad-spectrum antibiotic therapy, corticosteroids, heparin at a curative dose and on antifungal (Anidulafungin 100mg) as a prophylactic on Day 0. Bacteriological and mycological blood cultures were negative. A Lumbar Puncture (LP) was performed on Day 4 showing hypoglycorrhachia at 1.9 mmol/l, hyperproteinorrhachia at 1.9 g/L and high cellularity at 11 white elements, 80% of which is lymphocytic. On Day 6, the culture of the LP isolated *C. guilliermondii* sensitive to antifungals (caspofungin, micafungin, voriconazole, amphotericin B and Flucytosin). However, the patient died on Day 6 from post-septic shock.

Laboratory information

The Cerebrospinal Fluid (CSF) was cultivated on Sabouraud medium with and without Actidione and on CHROMagar Candida medium (CHROMagar, France). Yeast identification was done by chlamydosporulation test and YST- VITEK² card (bioMérieux, France). The antifungal susceptibility of the isolate was determined in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) by using AST- VITEK² Card [7].

DNA was extracted from pure cultures and nucleotides of Internal Transcribed Spacer 1 (ITS 1) were sequenced as described previously [3]. Sequence was analyzed using Bio Edit, version 7.2.0 (<http://www.mbio.ncsu.edu/bioedit/bioedit.html>) to confirm the taxa-specificity of the selected species.

Results

Culture on CHROMagar revealed pink colony and on Agar Actidione agar it shiny beige and mucous (Figure 1). The isolate showed short pseudo filament on chlamydosporulation test (Figure 2) and was identified *C. guilliermondii* by YST Vitek² Card. The strain was sensitive to all tested antifungals drugs (caspofungin, micafungin, voriconazole, amphotericin B and Flucytosin).

Discussion

Although, invasive *Candida* infections reported the highest

frequency of fungal infections, only 0.5% of the cases involved the CNS, making CM rather uncommon [8].

While the most common presenting symptoms of COVID-19 infection are fever and cough, there is a dramatic range of symptoms which can be associated with this syndrome. This paper disclosed that CM in the context of SARS-CoV-2 infection is a rare but life-threatening complication. We report the first case of CM associated to COVID-19 in Tunisian population and over the world.

Up to date, few studies reported meningitis and SARS-CoV-2 co-infection. This event represent 15.63% of cerebral trauma occurred in patients with COVID-19 [9]. In table 1 we have illustrated cases of meningitis and SARS-CoV-2 co-infection. Bacterial meningitis has been reported in the USA and South Africa where *Mycobacterium tuberculosis* had infected children aged 2 and 5 [10,11]. Also, in UK, *Escherichia coli* and *Neisseria meningitidis* were reported as a causative agent of meningitis in patients with SARS-Cov2 [12,13]. Cases of viral meningitis have also occurred. Turkish and Chinese studies show that SARS-COV-2 has been isolated from CSF [14-16] and an American paper reported case of Shingles [17].

Meningitis caused by *Candida* yeasts is due to numerous risk factors. Herein, SARS-CoV-2 infection induces an immunodepression state. In fact, immunological studies approved a low absolute number of T lymphocytes, CD4+T and CD8+T cells, in severe COVID-19cases than moderate cases, associated with markedly higher levels of IL-2R, IL-6, IL-10, TNF-alpha and some other inflammatory markers [18]. The high aggressive feature of the SARS-CoV-2 virus to the lung tissue that make the occurrence of invasive fungal infection very likely [18].

In addition, the infection of the CNS in our patient can be probably a consequence of hematological dissemination of the yeast which can be suggested by hepatic abscesses revealed on CT-scan. But unfortunately, the liver biopsy was not performed. We cannot exclude this possibility even in presence of a negative Blood culture. As described by Fabre V, et al., most blood cultures in clinical practice do not grow organisms [19].

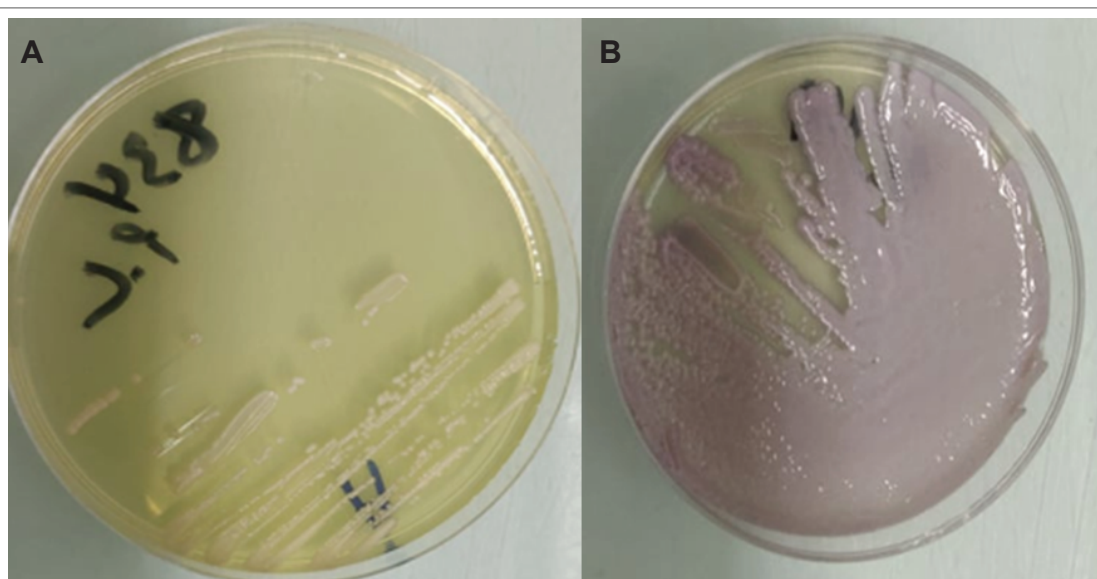


Figure 1: A Culture of *Candida guilliermondii* on sabouraud chloramphenicol medium supplemented with actidione (A) and on Chromagar[®] medium (B).

Table 1: Clinical characteristics of Meningitis associated to SARS-COV-2 infection.

Age/Gender	Background	Symptoms	Species	Treatment	Outcome	Country	Reference
Bacterial Meningitis							
2.7 y/F	Decreased appetite Enlarging cervical lymphadenopathy	Weakness Lethargy	<i>Mycobacterium tuberculosis</i>	Isoniazid Rifampicin Pyrazinamide Ethionamide Prednisone	Recovered	South Africa	[10]
5y/F	ND	Fever Headache	<i>Mycobacterium tuberculosis</i>	Oral hydroxychloroquine Azithromycin	Dead	USA	[11]
70y/F	Hypertension	Fluctuating cognition Headache Fever	<i>Escherichia coli</i>	Intravenous amoxicillin Intravenous ceftriaxone	Recovered	UK	[12]
22y/F	No medical history	Fever Headache Neck stiffness Confusion	<i>Neisseria meningitidis</i>	Intravenous ceftriaxone	Recovered	UK	[13]
Viral Meningitis							
59 y/M	Hypertension, diabetes, obesity	Consciousness disturbance, delirium	SARS-COV-2	Plasmapheresis treatment, AZI, HC, FAV	Dead: Cardiac arrest	Turkey	[14]
51/F	Hypertension, diabetes,	Consciousness disturbance, delirium	SARS-COV-2	Plasmapheresis treatment, AZI, HC, FAV	Recovered	Turkey	[14]
55/M	Hypertension	Consciousness disturbance Delirium	SARS-COV-2	Plasmapheresis treatment Azitromisin Hydroxychloroquine Faviripavir	Recovered	Turkey	[14]
56/M	ND	Consciousness confusion	SARS-COV-2	ND	Recovered	China	[15]
64/M	ND	Lethargic, unresponsive	SARS-COV-2	Oxygen inhalation, Arbidol, Ribavirin, Traditional Chinese medicine	Recovered	China	[16]
58/M	Hyperlipidemia	Headache, fever, abdominal pain, and constipation	<i>Shingles</i>	ND	Recovered	USA	[17]

y: year; ND: Not defined; M: male; F: Female; SARS-COV-2: Severe acute respiratory syndrome coronavirus

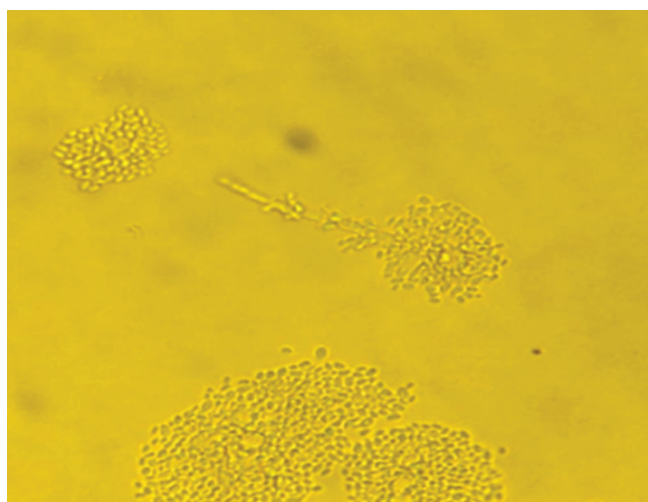


Figure 2: Chlamydosporulation test of *Candida guilliermondii* yeast showing a short pseudofilament.

In our current case, the patient was a female of 47 year old. In the literature, age may not play as significant in assessing risk for meningitis in COVID-19 patients. Incidence reported previously indicates that aggressive neurologic damage affects young patient as well as old patients [10,11,14].

CSF findings were consistent with those reported before suggest a similar aspect to Cryptococcal or *Mycobacterium tuberculosis* meningitis. In this case, CFS was positive for *C. guilliermondii*. Most cases of CM are due to *C. albicans*, with few reports of *C. glabrata* and other species causing infection. In meningitis, infection by *C. guilliermondii* is exceedingly rare. Epidemiological statistics from China and Japan reports prevalence of 1/785 and 1/27 respectively [6,20].

This yeast belongs to the normal fungal microbiota of human skin and mucosa [21]. It is an uncommon species of *Candida* spp that is most often associated with onychomycosis [22]. However, it has been documented to cause infection in immunocompromised patients undergoing surgical procedures, endocarditis in intravenous drug users and fungemia [21,23,24]. It has also been isolated in urinary tract

infections [20]. In this paper we describe the first case of meningitis caused by *C. guilliermondii* occurred in patient with SARS-CoV2 virus.

Despite new cases of low susceptibility to polyenes and Echinocandins [25], our strain isolated from the CSF culture was fully susceptible *in vitro* to caspofungin, micafungin, voriconazole, amphotericin B and Flucytosin. Sensitivity towards Fluconazole wasn't tested by AST Card regarding described acquired resistance to this molecule [26].

The evolution in our case was fatal despite the patient received 6 days of antifungal treatment and the sensitivity of the yeast for antifungals. In general, the mortality of CM is high [4]. Likewise, in two independent studies from Chinese hospitals, 27 of 28 (96.4%) and 11 of 68 (16%) COVID-19 patients who died had secondary infections [27]. The presence of neurological disease in patients with SARS-CoV2 virus is associated with higher mortality [9]. However, this is in contrast to other published case reports were COVID-19 patients with encephalitis or meningitis improved after systematic treatment [10,14,17].

Our patient received 6 days of anidulafungin as prophylactic treatment. Due to the high morbidity of CM, its management remains one of the most controversial issues in ICU. In patients with or without COVID-19, reports have demonstrated the use of Echinocandins as a choice of initial management [2]. However, others reports suggest the use of amphotericin B with or without flucytosine in first line treatment [4]. Fluconazole, voriconazole, posaconazole or/and isavuconazole is recommended as the second line alternatives [2,4,28].

Conclusion

We believe that our paper provides valuable information, adding to the literature a detailed case with COVID-19 infection who also developed cerebral co-infection.

In summary, SARS-CoV-2 may mask or worsen *Candida* infection. Thus clinicians and microbiologists should be vigilant for the risk of developing CM in patients with co-existing COVID-19 infection.

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Conflict of Interest

The authors declare that they have no competing interests

Ethical Approval

No formal ethical approval was required for this work, as it is a systematic analysis for the patient during her hospitalization.

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