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Case Report

# Cryptococcuria Without the Disseminated Disease

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Here we present two patients with COVID-19 infection, who were diagnosed with isolated Cryptococcuria without the disseminated disease. Both patients were male with ages of 55 years and 80 years respectively. Serum cryptococcal antigen test and Human immunodeficiency virus (HIV) serology was found to be negative in both and both patients responded well with appropriate antifungal treatment, although cryptococcus has been known to cause infections in immunocompromised (particularly in HIV patients) it has also been reported to cause infections in immunocompetent individuals. It has high mortality and morbidity if left untreated or if the diagnosis is delayed.[1] Here we present two cases with the rare finding of Cryptococcus in urine causing urinary tract infection without disseminated diseases, in non-HIV patients, with COVID-19 infection.

## Case 1

A 55-year-old male; with a known case of diabetes, hypertension, and stage 5 Chronic Kidney Disease, presented in the emergency department with complaints of fever and cough for two days associated with drowsiness on and off for the last two months which had worsened since the last two days. He had a two-days history of hospitalization in another hospital with similar complaints before coming to our emergency department. He had been previously diagnosed with severe aortic stenosis for which he had a bio-prosthetic aortic valve replacement two months back. On arrival in the emergency room, his blood pressure was 120/90, respiratory rate was 38 breaths per minute, heart rate was 102 beats per minute and temperature was 38 degrees centigrade. He was confused and had a Glasgow Coma Score (GCS) of 14 out of 15. There was no neck rigidity or any other signs of meningeal irritation. Pupils were bilaterally reactive to light, planters were down going and power was 5/5 in all four limbs. All other systemic examination was unremarkable.

A non-contrast Magnetic Resonance Imaging (MRI) of the brain had been done before arrival in ER which was normal and cerebrospinal fluid studies were performed which showed raised white cell count with lymphocytic predominance. Given the ongoing COVID-19 outbreak and suggestive symptoms; a nasal swab for SARS-Cov-2 PCR (polymerase chain reaction) was sent which was positive.

A chest X-ray was done which was normal and he had no oxygen requirement so he was classified as a non-severe COVID-19 infection based on WHO clinical criteria.[2] His sputum was sent for gram stain and culture/sensitivity and a good quality specimen grew Colistin-resistant Klebsiella pneumoniae and Stenotrophomonas maltophilia possibly reflective of his recent hospitalization As part of the workup for fever and suspected urinary tract infection due to recent catheterization; a urine culture was sent which showed Cryptococcus neoformans and Klebsiella pneumoniae. Blood cultures were negative. C-reactive protein was 34 mg/l and serum procalcitonin was negative. i.e. 0.2ng/ml. A serum cryptococcal antigen was negative as was the HIV serology.



His blood urea nitrogen (BUN) was 106mg/dl at presentation. He underwent hemodialysis and the BUN gradually decreased to 36 mg/dl though this did not improve his altered mentation. A repeat MRI with Angiography imaging was performed which showed moderate supratentorial hydrocephalus with periventricular cerebrospinal fluid seepage along with focal microhemorrhages in the left frontal and parietal lobes with minimal intraventricular hemorrhage. However, no acute infarct or hemorrhage was present.

The Cerebrospinal fluid analysis (CSF) was performed which showed increased protein (106mg/dl) along with a raised total leukocyte count (0.352 10×3/uL) lymphocytes predominance but a normal glucose (49 mg/dl with corresponding serum glucose of 89 mg/dl). There was no growth in culture. Herpes Simplex Virus PCR was negative in the CSF as was a film array multiplex PCR (including for cryptococcus). Similarly, a COVID-19 PCR and cryptococcus antigen test, and India ink

test were also negative in the CSF. However, Anti NMDA (N-methyl-D-aspartate) antibodies were detected in CSF.

For Cryptococcuria, initially, intravenous Amphotericin deoxycholate was given for 11 days and later treatment was continued with oral fluconazole for 6 months in renal adjusted doses. The patient was also treated with oral co-trimoxazole for Stenotrophomonas maltophilia and with intravenous Colistin for Klebsiella pneumoniae. Five sessions of plasmapheresis were done for autoimmune encephalitis. The patient significantly improved and became afebrile and hemodynamically stable. At the last follow-up at 21-week post-discharge, the patient was on his 6 months of fluconazole treatment and is now subjectively as well as clinically better.

## Case 2

An 80-year-old male patient with known co-morbid of hypertension, ischemic heart disease, and a history of Coronary Artery Bypass Graft (CABG) in 2016. He had a history of critical Covid 19, three months before presentation in the clinic, he had not recovered completely as generalized weakness was persistent on presentation in the clinic with additional complaints of low-grade undocumented fever, continuous, resolved by taking antipyretics, associated with burning micturition since 15 days. He had a history of taking multiple antibiotics for his fever but his symptoms didn't resolve. He had received intravenous tocilizumab, and systemic steroids as well as a session of plasmapheresis when had COVID-related ARDS, 3 months earlier. On initial assessment in the clinic, his blood pressure was 125/61mm of Hg, pulse was 88 beats per minute, respiratory rate was 18 breaths per min and he was afebrile. His systemic examination was unremarkable.

Initial workup including CBC, CRP, and serum procalcitonin was within normal limits. A urine analysis was performed and the culture grew Cryptococcus neoformans. His blood culture, HIV serology, and serum cryptococcal antigen were negative. Given the lack of neurologic complaints, a CSF analysis was not performed.

He was treated with oral Fluconazole for cryptococciuria and became afebrile after 3 days of starting fluconazole. The patient improved clinically and a plan was to continue antifungal therapy for 6 months with monthly clinic follow-ups. On a follow-up clinic visit, at 27 weeks after completing the fluconazole course of 6 months, he is subjectively doing well and clinically better.

## Discussion

We describe 2 cases of isolated Cryptococcus neoformans in urine culture without disseminated disease, associated with COVID -19 infection. Cryptococcus neoformans is transmitted to humans mostly by inhalation. Patients with abnormal cell-mediated immunity (such as HIV and solid organ transplant recipients) are predisposed to infections with this organism. However, infections can also occur rarely in apparently immunocompetent persons as well.[3] There have been few case reports of Cryptococcus infection in non-HIV patients. Poley et.al reported a case of a 37-year-old immunocompetent man with Cryptococcus neoformans meningitis.[4] Two cases from India have also been reported of cryptococcal meningitis in an HIV-negative 20-year-old young pregnant lady and 18-year- old male with multiple skin lesions.[5] There have been few proposed mechanisms and underlying pathology recognized in patients who are negative for HIV and not on immunosuppressives. These include Idiopathic CD4 lymphocytopenia (ICL) with relative CD4 deficiency in the absence of HIV infection[5,6] or even poor glycaemic control such as in a patient with diabetes as reported by Owuor et al. in a 27-year- old, non-HIV, African lady with Cryptococcal meningitis.[7] Covid 19 associated invasive fungal infection has been a known entity now, and the incidence of pulmonary aspergillosis is significantly high (2% to 33%), 8 later incidence of mucor-mycosis (0.3% co-infection) has also been reported.[9] However, only a few cases have been reported of the incidence of Cryptococcus neoformans with Cryptococcemia in association with Covid 19.[10,11] The proposed mechanism of fungal infection in association with Covid 19 is immune system dysregulation by the virus and immunomodulatory therapy used in the management of Covid 19 infection.[8] Our indexed cases are the first to report the incidence of Cryptococcuria without disseminated disease in Covid 19 patients.

Cryptococcus mainly causes central nervous system infections whereas the lungs are the most common extranervous system site to be affected.[12] On the other hand, Cryptococcus in urine has rarely been recognized in clinical practice. Xu et al. reported a case of pulmonary and prostate cryptococcosis in a patient with HIV which was initially misdiagnosed as tuberculosis.[13] Muranda et al. reported a Cryptococcoma in a 30-year-old renal transplant patient in which a biopsy of the lesion in the transplanted kidney demonstrated infection with Cryptococcus.[14] A retrospective observational study conducted by Kiertiburanakul et al. on patients with positive urine culture for Cryptococcus neoformans from 1992 to 2003 identified 16 patients of which 56% of patients were male, with a mean age of 44 +/- 21 years. Most of the patients had underlying conditions such as HIV, diabetes mellitus, hypertension, and/or systemic lupus erythematosus. The majority of the patients had cryptococcuria as a manifestation of disseminated cryptococcosis and only 19% had isolated cryptococcuria. This is similar to our patients with COVID-19 who had

isolated cryptococcuria without apparent dissemination. Nine (56%) patients in the Kiertiburanakul et al. study received antifungal therapy and other patients were not able to receive the antifungal treatment as they expired before the diagnosis was made. The mortality rate was up to 64% in this study, and the cause of death was disseminated cryptococcal infection or concomitant opportunist infections.[15]

The two cases of cryptococcemia associated Covid 19 are worth mentioning, the first case received a high dose of tocilizumab along with intravenous steroids and the other case was of a renal transplant patient with underlying liver cirrhosis, both had covid -19 and later developed cryptococcemia. These cases had an unfortunate course, both died within 10 days and 21 days, despite treatment with intravenous treatment with amphotericin and fluconazole, respectively.[10,11]

## Conclusion

The reporting of these cases aimed towards inciting further research in this regard to develop guidelines for antifungal treatment and duration. Moreover, high Clinical suspicion index needed to diagnose isolated Cryptococcuria as late or misdiagnosis leads to poor outcomes, hence these two index cases are being reported to increase awareness among clinicians, especially while managing Covid -19 patients.

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