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Case Series

Microbiology Section

Cryptococcal Meningitis in Post-COVID Era: A Case Series

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ABSTRACT

Meningitis, defined as inflammation of the meninges surrounding the brain and spinal cord, can arise from a broad spectrum of infectious and non infectious causes. Among infectious aetiologies, fungal meningitis is less common but poses significant morbidity and mortality. Cryptococcal meningitis, a life-threatening fungal infection primarily affecting immunocompromised individuals, has shown an increased incidence in the post-Coronavirus Disease-2019 (COVID-19) era. Immune dysregulation caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the widespread use of immunosuppressive therapies are suspected contributors to this rise. The first case was a 47-year-old Human Immunodeficiency Virus (HIV)-positive man on tuberculosis treatment who presented with meningitis symptoms; India ink preparation showed a yeast cell with a refractile halo. The second case was a 75-year-old man with a prior COVID-19 infection who developed meningitis and was diagnosed with cryptococcal meningitis. The third case was a 37-year-old asthmatic female on steroids with a history of COVID-19 who presented with headache and altered sensorium. Cerebrospinal Fluid (CSF) was collected and sent for investigation. India ink showed encapsulated yeast cells and culture showed Gram-positive budding yeast cells. The fourth case was a 50-year-old male with chronic kidney disease who presented with fever, neck stiffness and altered sensorium. Gram stain of CSF and India ink preparation both showed *Cryptococcus*. All patients were treated with amphotericin B and fluconazole, with favourable clinical outcomes. Clinicians should maintain a high index of suspicion for opportunistic fungal infections in patients with recent COVID-19 or immunosuppressive therapy.

Keywords: *Cryptococcus*, Fungal infections, Immunocompromised

INTRODUCTION

Meningitis refers to inflammation of the leptomeninges and the CSF within the subarachnoid space. It can be caused by a wide range of infectious agents, including bacteria, viruses, fungi and parasites, as well as by non infectious processes such as autoimmune disorders and malignancies. The clinical presentation typically includes fever, headache, neck stiffness and varying degrees of altered consciousness; however, these signs can be subtle or absent in immunocompromised individuals [1].

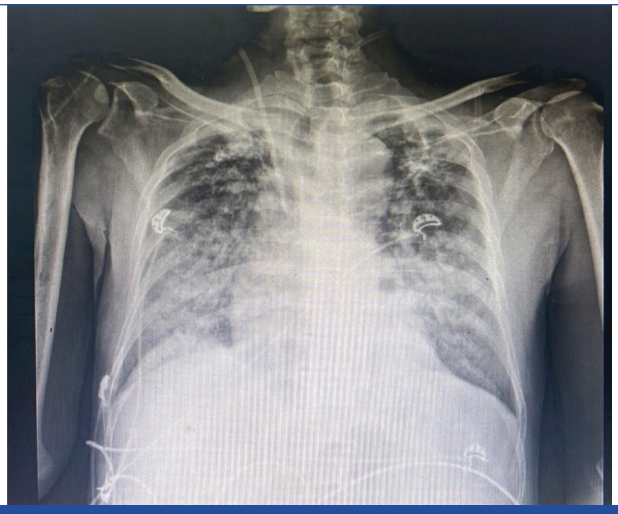
Cryptococcal meningitis is a subacute or chronic meningoencephalitis caused primarily by Cryptococcus neoformans, a ubiquitous environmental yeast that primarily affects individuals with impaired cell-mediated immunity. Although historically associated with advanced HIV infection, especially in resource-limited settings, its epidemiology has broadened to include solid organ transplant recipients, patients on long-term corticosteroids and more recently, those with COVID-19-related immune dysregulation. The pathogenesis involves inhalation of the organism, pulmonary colonisation and subsequent haematogenous dissemination to the central nervous system. Once in the CNS, the organism's polysaccharide capsule and melanin production play critical roles in immune evasion and neurotropism [2]. Centers for Disease Control and Prevention (CDC) estimates that nearly one million cases of cryptococcal meningitis occur globally each year, with six lakh deaths within three months of infection [3].

SARS-CoV-2 triggers significant immune dysregulation, disrupting both innate and adaptive immunity. This imbalance is marked by an excessive release of cytokines, including tumour necrosis factor and interleukins (particularly IL-1 and IL-6), which fuel an uncontrolled inflammatory response and potentially cause widespread tissue damage [4]. In severe cases, Natural Killer (NK) cell activity is notably diminished, weakening the body's ability to rapidly target infected cells. Additionally, T-cell dysfunction and impaired antiviral immunity hinder effective viral clearance, while the virus itself may contribute to immunosuppression, further compromising host defence mechanisms [5]. As a consequence, COVID-19 patients face an increased risk of latent disease reactivation and opportunistic infections [6,7]. The widespread use of immune-modulating therapies, coupled with virus-induced immunosuppression, has led to a concerning rise in fungal infections. This growing complication has significantly contributed to higher mortality rates among COVID-19 patients [8-12]. Out of the 19 cases screened in Tripura Medical College and DR. BRAM Teaching Hospital for cryptococcal meningitis over a span of two years (2022–2024), four cases were confirmed.

CASE SERIES

Case 1

A 47-year-old man, known to be pulmonary tuberculosis positive and on antitubercular therapy for six months, presented with headache for four days and fever on and off for two days. He also had dry cough, weight loss, vomiting, loose stools and progressive fatigue of two weeks' duration. After admission he was diagnosed as HIV seropositive. No documented history of COVID-19 exposure. No other medical or family history. On assessment, vitals were as follows: SpO_2 94% on room air, body temperature 101°F, heart rate 84/min, blood pressure 100/70 mmHg, and respiratory rate 34/min. Respiratory system examination revealed bilateral basal crepitations as shown in [Table/Fig-1]. The provisional diagnosis was meningitis. Lumbar puncture was performed. Laboratory investigations are shown in [Table/Fig-2]. Final diagnosis based on the investigations was cryptococcal meningitis. Treatment was started based on Infectious Diseases Society of America (IDSA) and World Health Organisation (WHO) recommendations; the patient was started on induction phase with intravenous amphotericin B (1 mg/kg/day) plus high-dose fluconazole 800 mg/day orally for two weeks, consolidation phase with fluconazole 400 mg/day orally for eight weeks, followed by maintenance phase for one year with fluconazole 200 mg/day orally. This regimen was followed because the patient was HIV seropositive. The patient responded well to



[Table/Fig-1]: Chest X-ray of case no.1 shows bilateral infiltration resembling pneumonitis.

Fig-2]. Final diagnosis based on the investigations was cryptococcal meningitis. The patient was started on intravenous amphotericin B (1 mg/kg/day) and fluconazole 800 mg orally for two weeks and he showed a good response. After two weeks of treatment, he was discharged on fluconazole 200 mg/day orally for four weeks. On follow-up after one month, his complete blood count had returned to normal and his lymphocyte count also improved.

Case 3

A 37-year-old female with a history of bronchial asthma on inhaled corticosteroid therapy was admitted to the medical ward with a two-week history of headache and altered sensorium. She had a past history of COVID-19 infection six months earlier, for which she was admitted to hospital. No other medical or family history was noted. On examination, she was conscious but disoriented. Her pulse rate was 82 beats/min, blood pressure 120/70 mmHg, and oxygen saturation 96% on 2 L/min of oxygen. Respiratory examination revealed bilateral wheeze. The provisional diagnosis was meningitis. A lumbar puncture was performed. Laboratory

Laboratory parameters	Case 1	Case 2	Case 3	Case 4
Complete blood count	White cell count 3.1×10^9/L; neutrophils 50%; lymphocytes 46%; monocyte 1%; eosinophil 3%; Red blood cells 4.8 × 10^{12}/L; Haemoglobin 6.1 g/dL; Platelets 133 `X 10^9/L CD4 count was 150 cells/µL	White cell count 5.8×10^9/L; neutrophils 80%; lymphocytes 14%; monocyte 1%; eosinophil 5%; Red blood cells 4.5 × 10^{12}/L; Haemoglobin 11 g/dL; Platelets 166×10^9/L. From his previous CBC report the patient showed persistent lymphopenia one month after COVID-19 recovery	White cell count 7.8×10^9/L; neutrophils 72%; lymphocytes 22%; monocyte 1%; eosinophil 5%; Red blood cells 4.5 × 10^{12}/L; Haemoglobin 13 g/dL; Platelets 185×10^9/L	White cell count 6.4×10^9/L; neutrophils 74%; lymphocytes 20%; monocyte 2%; eosinophil 4%; Red blood cells 4.0 × 10^{12}/L; Haemoglobin 10 g/dL; Platelets 155`X 10^9/L
Biochemistry parameters	Random blood sugar 124 mg/dL; Urea 34 mg/dL; Creatinine 1.8 mg/dL; Sodium 137 mmol/L; Potassium 4.1 mmol/L; Calcium 7.2 mg/dL; Albumin 3.4 gm/dL; Magnesium 2 mg/dL. Hepatic panel: Bilirubin total 1.2 mg/dL and Direct 0.5 mg/dL; Alanine transaminase 53 units/L; Aspartate transaminase 47 units/L; Alkaline phosphatase 76 IU/L	Random blood sugar 96 mg/dL; Urea 32 mg/dL; Creatinine 0.5 mg/dL; Sodium 135 mmol/L; Potassium 3.6 mmol/L; Calcium 8 mg/dL	Random blood sugar 68 mg/dL; Urea 30 mg/dL; Creatinine 0.7 mg/dL; Sodium 135 mmol/L; Potassium 3.5 mmol/L; Calcium 9 mg/dL	Random blood sugar 82 mg/dL; Urea 42 mg/dL; Creatinine 3.5 mg/dL; Sodium 138 mmol/L; Potassium 3.5 mmol/L
Serology	Widal test, MP optimal, Scrub typhus were negative	Widal test, MP optimal, Scrub typhus were negative	Widal test, MP optimal, Scrub typhus were negative	Widal test, MP optimal, Scrub typhus were negative
CSF examination	Biochemistry: CSF protein 40 mg/dL, CSF chloride 103.3, CSF glucose 107 mg/dL,ADA-10U/L Pathology: Red blood cells= 6/mm^3 with predominant lymphocytes. Microbiology: CSF was microbiologically confirmed by India Ink Prepration showed yeast cell with refractile halo seen representing *Cryptococcus* species, [Table/Fig-3a], Fungal culture showed creamy off white pasty colony [Table/Fig-3c], which on gram stain showed budding yeast cell [Table/Fig-5a], Urease test was done from the colony which came positive as shown in [Table/Fig-3d]	Biochemistry: Protein level is high (280 mg/dL), while Sugar level is low (8 mg/dL). Pathology: All lymphocytes. Microbiology: India ink preparation showed yeast cell with refractile halo [Table/Fig-4a], CSF Gram staining showed gram-positive round budding yeast [Table/Fig-5b], CSF culture yielded Cryptococci and urease test was positive as shown in [Table/Fig-3e]	Biochemistry: CSF protein was 100 mg%, Sugar 49 mg% with corresponding RBS 169 mg% Pathology: Total cell count 1500 cells/cu.mm, all were lymphocytes Microbiology: CSF gram stain revealed gram positive yeasts [Table/Fig-5c], and India ink showed many cryptococci with negative staining capsule [Table/Fig-4b], and nigrosin stain showed encapsulated yeast cell as shown in [Table/Fig-3b]	Biochemistry: CSF protein was 150 mg%, Sugar 45 mg% Pathology: Total cell count 1800 cells/cu.mm, all were lymphocytes Microbiology: CSF gram stain revealed gram positive yeasts [Table/Fig-5d], and India ink showed cryptococci with a refractile halo as shown in [Table/Fig-4c] Fungal culture on SDA showed creamy white colonies [Table/Fig-2f]
Non Contrast Computed Tomography (NCCT) brain	No abnormality as shown in [Table/Fig-6a].	Not done because of financial constraint.	No abnormality as shown in [Table/Fig-6b].	Not done as patient was very irritable.

[Table/Fig-2]: Laboratory investigations of all four case scenarios.

treatment and was discharged after four weeks. At one-month follow-up, his complete blood count and CD4 count had increased and other biochemical parameters were normal, with symptomatic improvement.

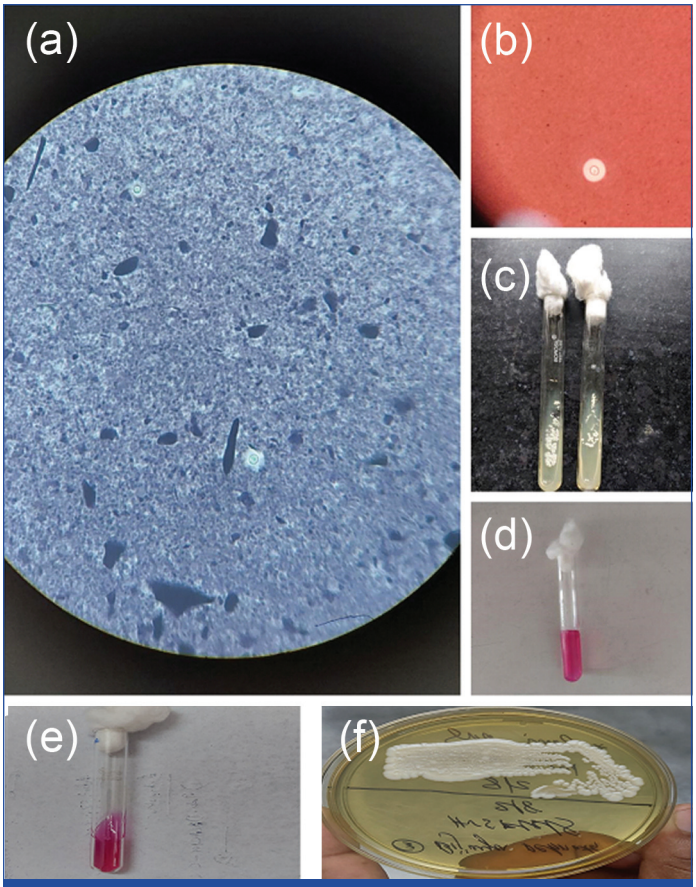
Case 2

A 75-year-old male was admitted with a history of headache and vomiting for one month. He had a history of COVID-19 infection two months earlier. On examination, he was conscious but disoriented. His pulse rate was 68 beats/min, blood pressure was 110/70 mmHg, and saturation was 99% in room air. No other medical or family history. The systemic examinations were within normal limits, except for neck stiffness. The provisional diagnosis was meningitis. Lumbar puncture was performed. Laboratory investigations are shown in [Table/

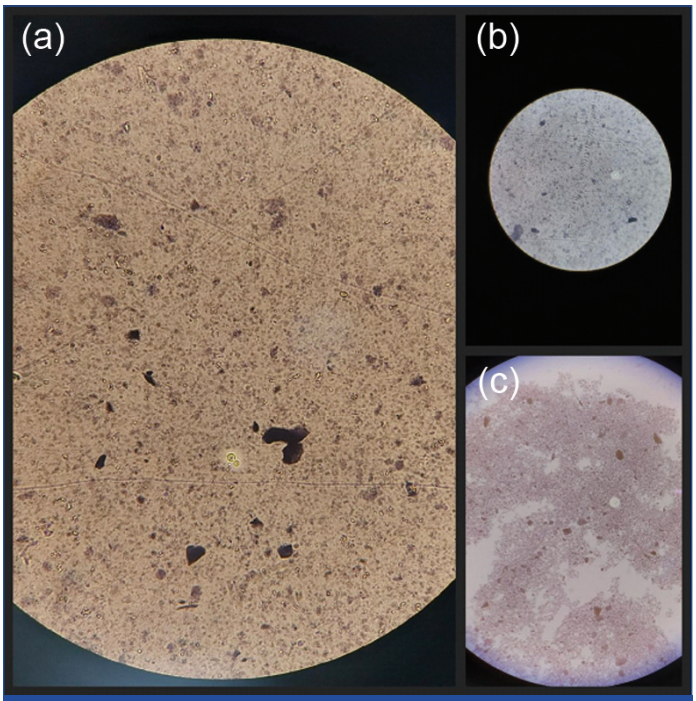
investigations are shown in [Table/Fig 2]. The final diagnosis based on the investigations was cryptococcal meningitis. The patient was started on intravenous amphotericin B and fluconazole 800 mg/day orally for two weeks as induction therapy, followed by fluconazole 400 mg/day for eight weeks as maintenance therapy. After 10 weeks of treatment, she responded well and was discharged. On follow-up after one month, her complete blood count and other biochemical parameters were normal, and she had no new complaints.

Case 4

A 50-year-old male with known chronic kidney disease was admitted to the medical ward with fever for 10 days, neck stiffness and altered sensorium. He was irritable. There was no documented history of COVID-19 infection in the past. No other medical or family history

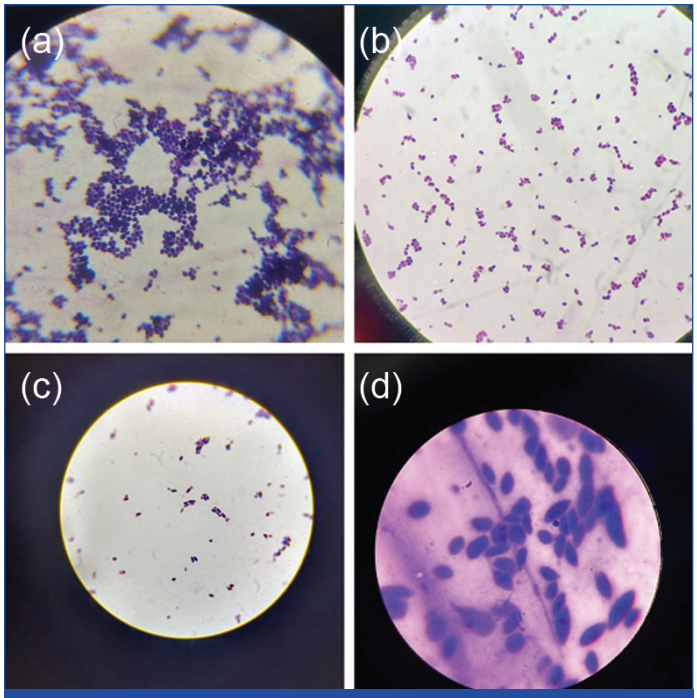


[Table/Fig-3]: a) India ink preparation (40x) of CSF shows encapsulated yeast cell. b) Nigrosin preparation (40x) of CSF shows capsule of *Cryptococcus neoformans*. c) Fungal culture of CSF on Sabouraud's Dextrose Agar (SDA) showing creamy pasty white colony. d) Positive urea hydrolysis test; e) Positive urea hydrolysis test; f) Fungal culture on SDA showing creamy white colony.
a, c - Case 1 b - Case 3 c - Case 2 d - Case 1 e - Case 2 f - Case 4

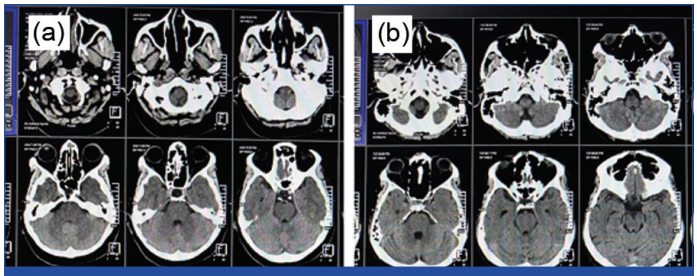


[Table/Fig-4a-c]: Belongs to case 2,3,4, respectively. India ink preparation (40x) of CSF shows encapsulated yeast cell.

was noted. On examination, he was conscious but disoriented. His pulse rate was 86 beats/min, blood pressure 140/70 mmHg and oxygen saturation was 98% on room air. The provisional diagnosis was meningitis. A lumbar puncture was performed. Laboratory investigations are shown in [Table/Fig-2]. The final diagnosis based on the investigations was cryptococcal meningitis. The patient was started on intravenous amphotericin B (1 mg/kg/day) plus flucytosine (25 mg/kg/day) orally in two divided doses for two weeks.



[Table/Fig-5]: a) Case 1; b) Case 2; c) Case 3; d) Case 4 Gram stain (100x) revealed Gram positive budding yeast cells.



[Table/Fig-6]: a) Case 1; b) Case 3; NCCT Brain shows no abnormality.

The patient responded well to treatment after two weeks and was discharged. On follow-up, all haematology parameters were normal and liver function tests were within normal limits.

DISCUSSION

The landscape of infectious diseases has undergone a significant transformation in the post-COVID era. The aetiologies, pathophysiology and clinical presentations of various syndromes have evolved, necessitating a broader and more dynamic diagnostic approach. Clinicians must now consider an expanded spectrum of differential diagnoses and tailor investigations accordingly to account for these emerging patterns. Authors encountered four cases of cryptococcal meningitis presenting with fever, headache and altered behaviour. Upon evaluation, only one patient had a known predisposing condition—an undiagnosed HIV infection, which was identified during the workup for meningitis. In HIV-infected individuals, the Th1/Th2 balance is disrupted, with increased IL-4 activity and reduced IFN-γ response. Additionally, CD4+ T cell–mediated granulysin-dependent killing of *Cryptococcus* is impaired, contributing to disease susceptibility [13,14].

The use of immunosuppressants in COVID-19 treatment has been linked to an increased risk of opportunistic infections. Various fungal infections have been reported due to immune modulation caused by therapies such as corticosteroids and JAK inhibitors [15,16]. Another report was on a patient with cryptococcemia in COVID-19 infection, who received tocilizumab and high-dose steroids [17]. Ghanem H and Sivasubramanian G, reported a case of severe cryptococcal meningitis that developed in a previously healthy patient one week after treatment of SARS-CoV-2 infection with dexamethasone [18]. As shown in [Table/Fig-7], a comparative analysis of cryptococcal meningitis case series reveals variations in outcomes across studies [17-19].

Study/ location	Publication year	Total cases (confirmed)	Immunocompromised status	Risk factors identified	Key findings
Tripura Medical College (Current study)	2025	4	1 HIV+, 1 post-COVID, 1 on inhaled steroids, 1 CKD	HIV, COVID-19, chronic steroids, CKD	Cryptococcal meningitis in post-COVID patients without classical immunosuppression
Ghanem H and Sivasubramanian G [18] (USA)	2021	1 (case report)	No known immunosuppression	Recent COVID-19, dexamethasone therapy	Cryptococcal meningitis in previously healthy male post-COVID
Khatib MY et al., [17] (Qatar)	2021	1 (case report)	No HIV, but COVID-19 with immunosuppressants	Tocilizumab + steroids	Cryptococcaemia reported in COVID-19 patient postimmunotherapy
Mitchell TG and Perfect JR (USA) [19]	1995 (Review)	>100 years review	Primarily HIV+ and transplant patients	CD4+ T-cell dysfunction	Pathophysiology of *Cryptococcus neoformans* immune evasion in AIDS patients

[Table/Fig-7]: Comparative analysis of cryptococcal meningitis case series across studies [17-19].

CONCLUSION(S)

Cryptococcal meningitis is a life-threatening condition that demands keen clinical vigilance and a collaborative approach between physicians and diagnosticians for timely detection and intervention. Clinicians should maintain a high index of suspicion for cryptococcal infection in COVID-19 patients, especially if they have received any immunosuppressive treatment.

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