JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

Fatal cryptococcal meningitis in an immunocompetent patient

Minoosh Shabani[1], Bahareh Bashardoust[2], Aleksandra Barac[3], Jianping Xu[4], Laura Alcazar-Fuoli[5], Ali Ahmadi[6], Sareh Montazeri[7], Sadegh Khodavaisy[8,9]

[1] Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Mycology and Parasitology, Faculty of Paramedicine, Golestan University of Medical Sciences, Gorgan, Iran.
[3] Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[4] Department of Biology, McMaster University, Hamilton, Ontario, Canada
[5] Mycology Reference Laboratory, National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain
[6] Department of Medical Parasitology and Mycology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7] Department of Parasitology and Mycology. School of Medicine, Zabol University of Medical Sciences, Zabol, Iran
[8] Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[9] Research center for antibiotic stewardship and antimicrobial resistance, Tehran University of Medical Sciences, Tehran Iran

Abstract

Introduction: Cryptococcal meningitis (CM) typically affects immunocompromised individuals and are commonly caused by *Cryptococcus neoformans*.
Case Report: We present CM case involving an immunocompetent male due to *Cryptococcus gattii* molecular type VGI.
Results: This case illustrates the diagnostic and management challenges associated with CM and emphasizes the need for continued vigilance in monitoring and understanding the epidemiology of cryptococcal infections in diverse patient populations.
Conclusions: Our case highlights the significant morbidity associated with cryptococcosis.

Key words: Cryptococcal meningitis; *Cryptococcus gatii*; immunocompetence.

J Infect Dev Ctries 2025; 19(6):977-981. doi:10.3855/jidc.17916

(Received 13 January 2023 – Accepted 05 December 2023)

Introduction

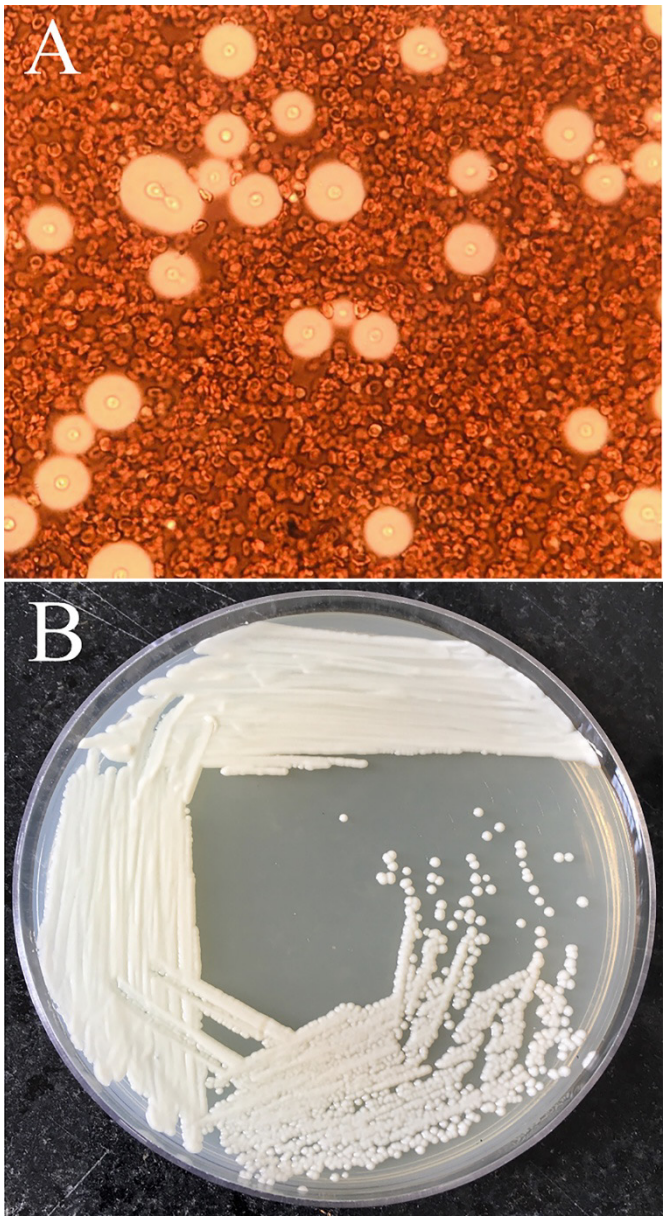
Cryptococcal meningitis (CM) is the most serious manifestation of Cryptococcosis caused by human pathogenic *Cryptococcus* that include both the *Cryptococcus neoformans* species complex and the *Cryptococcus gattii* species complex [1,2]. This infection generally occurs in immunocompromised individuals, especially HIV-AIDS patients in resource-limited countries [3-6]. It may cause significant morbidity, mortality, and long-term disability in the host. However, there have been increasing reports of CM in immunocompetent individuals, constituting an emerging threat to public health [7]. Effective treatment requires fast and accurate diagnosis and delayed diagnosis causes delayed or wrong treatment which can lead to the death of the patient. Recent outbreaks of cryptococcosis infections in healthy individuals have been documented across various geographical regions, including those caused by *C. gattii* in Canada and the Pacific Northwest of the US [8]. However, *C. gattii* infection is relatively rare in the Middle East. In this study, we present a case of CM caused by *C. gattii* in an immunocompetent patient in Iran.

Case Report

A 35-year-old male was admitted to the emergency department of Loghman-e Hakim in Tehran, Iran, with a severe headache. The patient appeared confused, making it difficult to obtain his past medical history directly. The patient's companion, who was present at the time of admission, provided valuable insights into his recent medical history. He resided in an urban area, was self-employed, and had no history of intravenous drug use or smoking or known allergies or significant

past medical or surgical history. There was no notable family history of immunosuppressive or neurological diseases, and other family members had not reported experiencing similar symptoms. Notably, the patient had brief, intermittent contact with pigeons for approximately two weeks. The patient had previously been hospitalized for approximately 20 days due to persistent headaches that had been ongoing for a month. These headaches did not respond to oral pain medications. Moreover, the patient had been experiencing fever, photophobia, and an altered mental state characterized by confusion and disorientation. Over time, the symptoms had progressively worsened.

Figure 1 A. Direct microscopic examination of Cryptococcus; **B.** Culture growth on SDA medium.



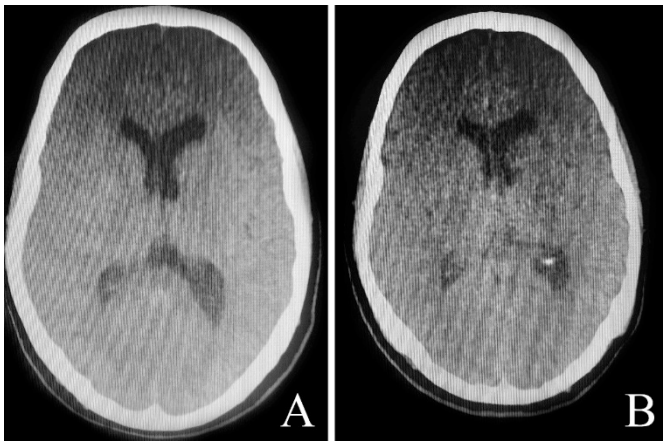
The patient reported increasing pain, partial hearing loss, blurred vision, as well as episodes of nausea and vomiting. Eventually, he lost consciousness. It's important to note that the patient did not experience any seizure episodes during this period. However, before the patient was referred to us, he was diagnosed with acute meningitis at another facility but the underlying cause was unknown. The initial treatment included ceftriaxone and sodium valproate. However, the disease continued to worsen, and the patient's symptoms did not show any improvement. Subsequently, the patient left the hospital with their consent and sought medical help in our department.

During the initial assessment, the patient was agitated and confused. He was awake but not alert nor oriented, with a Glasgow coma scale (GCS) of 12/15. Vital signs assessment demonstrated a blood pressure of 130/80, respiratory rate of 18, heart rate of 80, and a low-grade fever of 37.8. Bruises and needle marks were seen on the patient's arm, which were attributed to the previous hospitalization. There were no signs of petechia, purpura, or ecchymosis on other skin parts. Pupils were middle-size and reactive to the light despite the patient's agitation, with no signs of cervical tenderness or stiffness. Brudzinski and Kerning's signs were not significant and other physical examinations did not have any significant findings. The initial conservative treatment such as intravascular fluid resuscitation was administrated. A brain computed tomography (CT) scan without contrast and a spiral chest CT scan were administered and the brain CT scan was insignificant. Routine cerebrospinal fluid (CSF) and blood analysis were performed. The following differential diagnoses were performed, including subacute meningitis, partially treated acute meningitis, tuberculosis (TB), brucellosis, syphilis, and cryptococcosis. In addition to ceftriaxone and vancomycin, anti-TB was started because of the high incidence of TB as a chronic meningitis etiology in Iran. The analysis of venous blood gas (VBG) parameters in the patient indicated the following values at the first and last measurements, respectively: pH (7.5-7.47), pCO_2 (27.2-38.7 mmHg), pO_2 (58.7-98 mmHg), and HCO^{3-} (23.7-28.7 mEq/L). The test results showed an elevated blood urea nitrogen (BUN) level of 30 mg/dL and an elevated alanine aminotransferase (ALT) level of 78 U/L. The viral markers, including the human immunosuppressive virus antibody (HIVAb) and hepatitis B surface antigen (HBsAg), were confirmed as negative. Additionally, the immunologic and rheumatologic profiles showed a slightly elevated level of rheumatoid factor (RF). There was a mild increase in

bilirubin levels, characterized by a mixed pattern. Furthermore, the tuberculosis polymerase chain reaction (PCR) test yielded a negative result. Staining with India ink of the CSF sample revealed encapsulated budding yeasts (Figure 1A). Colonies grew fairly rapidly and were smooth, mucoid, and cream color on Sabouraud's Dextrose Agar (SDA, Difco) with chloramphenicol (50mg/L) after incubation at 37 °C for 48 hours (Figure 1B).

The CSF analysis results are summarized in Table 1. The first result revealed an absence of pleocytosis and a positive India ink stain. Consequently, the patient's previous medications were discontinued, and systemic liposomal amphotericin B (350 mg/day) and fluconazole (800 mg/day) were initiated. Unfortunately, the administration of flucytosine was hampered by financial constraints. In addition to antifungal treatment, chemical prophylaxis was initiated with subcutaneous heparin and pantoprazole. An electroencephalogram (EEG) was conducted, yielding results that did not reveal significant abnormalities. The patient was considered a candidate for a brain MRI; however, this procedure could not be carried out due to the patient's hemodynamic instability and agitation. Following the first CSF analysis, a notable upward trend in pleocytosis was consistently observed. Furthermore, the Indian ink test yielded positive results on each subsequent examination. Cryptococcal antigen (CrAg) detection using latex agglutination assay (LAA) and lateral flow assay (LFA) in CSF was positive. Molecular detection on CSF samples was positive for cryptococcosis by the multiplex PCR method [9]. Molecular identification was performed on growth colonies by sequencing the internal transcribed spacer region (ITS1-5.8S-ITS2) of the ribosomal RNA gene cluster [9]. The obtained sequence was compared with the GenBank database and identified as *C. gattii* molecular type VGI**,** showing 100% sequence identity with the ex-type strain of the species. The sequence with 581 bp length was deposited in GenBank with accession no. OR498641. Based on fungal laboratory findings, diagnosis of this CM case was made. Antifungal susceptibility testing was conducted using the broth microdilution method as outlined in the Clinical & Laboratory Standards Institute (CLSI) M27 4th document [10]. The minimum inhibitory concentrations (MICs) were determined as follows: amphotericin B (1 µg/mL), fluconazole (4 µg/mL), itraconazole (0.25 µg/mL), and voriconazole (0.125 µg/mL).

Figure 2. Brain CT scans. **A.** on admission; **B.** on day 5.



The patient was sedated and intubated and his head was elevated. The ventilator was set to a pCO_2 of 30-35 mmHg. In response to the increased intracranial pressure (ICP) as observed during the admission, the decision was made to initiate intrathecal injection of liposomal amphotericin B at a daily dose of 10 mg. During the patient's hospitalization, episodes of agitation were noted, raising concerns about further elevated ICP. To assess this, an additional spiral brain CT scan was conducted (Figure 2), confirming increased ICP. Consequently, acetazolamide therapy was promptly initiated. To address the ICP elevation associated with liposomal amphotericin B intrathecal injections, mechanical decompression was implemented using lumbar drains. On the seventh day of the admission, the patient became bradycardic, which led to cardiopulmonary arrest. Cardiopulmonary resuscitation was initiated, which was not successful, and the patient died.

Table 1. Cerebrospinal fluid *analysis during* the *admission.*

Parameter (unit)	Normal range	Day 1	Day 4	Day 6	Day 7	Day 8	Day 9
Appearance	Crystal clear	Semi-clear	Semi turbid	Semi turbid	Turbid	Semi-clear	Semi-clear
Color	Colorless	Pale yellow	Bright red	Semi bloody	Yellow	Yellow	Pale yellow
Opening pressure (cm H_2O)	5–20	22	21	22	21	25	25
RBC count (/µL)	0	200	1380	16000	4000	500	500
WBC count (/µL)	0–5	0	24	120	20	150	260
Polynuclear cell (%)	< 25	0	20	20	40	90	80
Mononuclear cell (%)	> 75	0	80	80	60	10	20
Glucose (mg/dL)	45–80	57	70	51	50	36	68
Protein (mg/dL)	15–45	53	44	136	65	70	63

Discussion

In this report, we present the clinical course and management of a case who presented with a severe headache, confusion, and other neurological symptoms, ultimately leading to a fatal outcome. The patient's complex clinical presentation, diagnostic challenges, and treatment decisions highlight the importance of considering unusual and opportunistic infections, especially in patients with subacute or chronic central nervous system (CNS) disease manifestations. In Iran, before this case, only two cases of CM infection in immunocompetent patients have been reported and both patients were successfully treated with a combination of liposomal amphotericin B and fluconazole and were eventually discharged from the hospital [11,12]. Our presented case involved another immunocompetent individual, a middle-aged man, whose age and clinical presentation were similar to the two previously reported cases. The patient complained of persistent severe headaches, vomiting, and nausea, leading to a diagnosis of CM. Following the protocol established in the previous cases, treatment commenced with liposomal amphotericin B and fluconazole. Despite these efforts, the patient's condition deteriorated, and expired. While timely and efficient administration of antifungal therapy has been established for managing CM [13,14], many additional factors, encompassing both clinical and laboratory information, can exert substantial influence on the overall prognosis of the condition [15]. The patient's initial CSF analysis revealed indicators of poor prognosis of CM, including positive India ink staining in the CSF, a high opening pressure upon lumbar puncture, and a CSF white blood cell (WBC) count of 0 cells/μL [16]. In the two earlier cases, the WBC counts were 20 cells/μL (20% polynuclear cells, 80% mononuclear cells) and 300 cells/μL (10% polynuclear cells, 90% mononuclear cells). The presence or absence of pleocytosis in these cases could potentially have significant implications for clinical outcomes. Moreover, standard medications won't work for infections caused by drug-resistant strains, making treatment more challenging and potentially leading to poor prognosis. In this case, the *Cryptococcus gattii* strain was resistant to amphotericin B but a standard antifungal medication was applied due to the delayed MIC result. Furthermore, the administration of flucytosine was hindered by financial constraints, emphasizing the significance of taking into account the availability and affordability of antifungal agents, particularly in resource-limited settings. This limitation may have played a key role in the unfavorable outcome of this case. Diagnosing CM can be challenging due to the extensive range of causes of meningitis that includes non-infectious factors such as malignancies, systemic diseases, and toxic exposures, as well as infectious agents, including opportunistic pathogens of bacteria, fungi, parasites, and viruses with variable and nonspecific neurological symptoms [17]. One of the main reasons for the missed opportunity for early diagnosis of cryptococcal etiology for meningitis here was a lack of knowledge or carelessness in differentiating acute meningitis from subacute and chronic forms. *Cryptococcus* usually causes subacute and chronic meningitis. In subacute and chronic meningitis, the interval between meningeal symptoms (including headache, fever, nausea, vomiting, photophobia, and neck stiffness) and the onset of meningitis complications (including loss of consciousness, symptoms of neurological deficit or seizures) are more than 5 and 14 days, respectively. As observed in the presented case, an initial diagnostic workup during the previous admission had led to a diagnosis of acute meningitis and inappropriate treatment. Due to the prevalence of tuberculosis in Iran, especially in people with healthy immunity, tuberculosis is the most common etiology of subacute and chronic meningitis, which can be another reason for delaying the diagnosis of CM [18]. The use of steroids in patients who continue to worsen on anti-tuberculosis treatment may cause rapid worsening of CM [19]. On the other hand, there are some differences in clinical features in CM and other chronic meningitis and CSF analysis results did not reliably distinguish one form of chronic meningitis from another [19]. The valuable finding in this case lies in the first-time isolation and identification of the *C. gattii* species from a human in Iran. All clinical isolates reported up to this point had been of the *C. neoformans* species [20]. The identification of *C. gattii* species in our study raises crucial questions about the shifting epidemiology of cryptococcosis in Iran and its potential implications for patient management. It is imperative to delve deeper into the factors contributing to the emergence of *C. gattii* species in this region, such as changes in host populations, environmental factors, or genotypic alterations within this pathogen.

In conclusion, this case illustrates the diagnostic and management challenges associated with subacute or chronic CM, particularly in immunocompetent individuals. It underscores the importance of considering unusual pathogens, obtaining a thorough environmental history, and addressing financial constraints in treatment decisions. Further research is needed to improve the diagnosis and management of

CM, especially in atypical presentations, to prevent fatal outcomes like the one observed in this case.

Acknowledgements

This study was supported by the Tehran University of Medical Sciences (grant No. 9711353001). We owe a great debt of gratitude to Loghman-e Hakim Hospital and its staff for their kind help.

Ethics approval

The presentation of this case was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1400.033), and written informed consent was obtained from the patient for publication of this report.

Corresponding author

Sadegh Khodavaisy
Department of Medical Parasitology and Mycology,
School of Public Health, Tehran University of Medical Sciences,
Tehran, Iran
Tel: +98-21-88008588
E-mail: sadegh_7392008@yahoo.com

Conflict of interests

No conflict of interests is declared.

References

1. Gushiken AC, Saharia KK, Baddley JW (2021) Cryptococcosis. Infect Dis Clin North Am 35: 493-514. doi: 10.1016/j.idc.2021.03.012.
2. Montoya MC, Magwene PM, Perfect JR (2021) Associations between *Cryptococcus* genotypes, phenotypes, and clinical parameters of human disease: a review. J Fungi 7: 260. doi: 10.3390/jof7040260.
3. Srichatrapimuk S, Sungkanuparph S (2016) Integrated therapy for HIV and cryptococcosis. AIDS Res Ther 13: 42. doi: 10.1186/s12981-016-0126-7.
4. Spec A, Powderly WG (2018) Cryptococcal meningitis in AIDS. Handb Clin Neurol 152: 139-150. doi: 10.1016/B978-0-444-63849-6.00011-6.
5. Bahn YS, Sun S, Heitman J, Lin X (2020) Microbe profile: *Cryptococcus neoformans* species complex. Microbiology 166: 797-799. doi: 10.1099/mic.0.000973.
6. Lakoh S, Rickman H, Sesay M, Kenneh S, Burke R, Baldeh M, Jiba DF, Tejan YS, Boyle S, Koroma C, Deen GF, Beynon F (2020) Prevalence and mortality of cryptococcal disease in adults with advanced HIV in an urban tertiary hospital in Sierra Leone: a prospective study. BMC Infect Dis 20: 141. doi: 10.1186/s12879-020-4862-x.
7. Kothiwala SK, Prajapat M, Kuldeep CM, Jindal A (2015) Cryptococcal panniculitis in a renal transplant recipient: case report and review of literature. J Dermatol Case Rep 9: 76-80. doi: 10.3315/jdcr.2015.1205.
8. Byrnes EJ 3rd, Marr KA (2011) The outbreak of *Cryptococcus gattii* in Western North America: epidemiology and clinical Issues. Curr Infect Dis Rep 13: 256-261. doi: 10.1007/s11908-011-0181-0.
9. Kord M, Salehi M, Khodavaisy S, Hashemi SJ, Daie Ghazvini R, Rezaei S, Maleki A, Elmimoghaddam A, Alijani N, Abdollahi A, Doomanlou M, Ahmadikia K, Rashidi N, Pan W, Boekhout T, Arastehfar A (2020) Epidemiology of yeast species causing bloodstream infection in Tehran, Iran (2015-2017); superiority of 21-plex PCR over the Vitek 2 system for yeast identification. J Med Microbiol 69: 712-720. doi: 10.1099/jmm.0.001189.
10. Berkow EL, Lockhart SR, Ostrosky-Zeichner L (2020) Antifungal susceptibility testing: current approaches. Clin Microbiol Rev 33: e00069-19. doi: 10.1128/CMR.00069-19.
11. Ghasemian R, Najafi N, Shokohi T (2011) Cryptococcal meningitis relapse in an immunocompetent patient. Arch Clin Infect Dis 6: 51-55.
12. Shokouhi S, Hakamifard A (2022) Meningitis caused by *Cryptococcus neoformans* in an apparently immunocompetent patient. J Investig Med High Impact Case Rep 10: 23247096221111779. doi: 10.1177/23247096221111779.
13. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR (2017) Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 17: 873-881. doi: 10.1016/S1473-3099(17)30243-8.
14. Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS (2017) Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 13: 13-24. doi: 10.1038/nrneurol.2016.167.
15. Tsai WC, Lien CY, Lee JJ, Lin WC, Hsu CW, Huang CR, Tsai NW, Chang CC, Lu CH, Chang WN (2018) The prognostic factors of HIV-negative adult cryptococcal meningitis with a focus on cranial MRI-based neuroimaging findings. J Clin Neurosci 55: 57-61. doi: 10.1016/j.jocn.2018.06.044.
16. Lu CH, Chang WN, Chang HW, Chuang YC (1999) The prognostic factors of cryptococcal meningitis in HIV-negative patients. J Hosp Infect 42: 313-320. doi: 10.1053/jhin.1998.0610.
17. Hildebrand J, Aoun M (2003) Chronic meningitis: still a diagnostic challenge. J Neurol 250: 653-660. doi: 10.1007/s00415-003-1101-5.
18. Mortazavi-Moghaddam SG, Pagheh AS, Ahmadpour E, Barac A, Ebrahimzadeh A (2022) Tuberculous meningitis and miliary tuberculosis in Iran: a review. Asian Pac J Trop Med 15: 143-152. doi: 10.4103/1995-7645.343880
19. Anderson NE, Willoughby EW (1987) Chronic meningitis without predisposing illness--a review of 83 cases. Q J Med 63: 283-95.
20. Bashardoust B, Alavi Darazam I, Daie Ghazvini R, Hashemi SJ, Salehi M, Abbasian L, Dehghan Manshadi SA, Abdorahimi M, Mohamadi A, Zamani F, Ardi P, Khodavaisy S (2020) Clinical and mycological implications of cryptococcal meningitis in Iran. Heliyon 2: e21395. doi: 10.1016/j.heliyon.2023.e21395.