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Case report

Cryptococcus meningitis presented with multiple cerebral infarcts in an immunocompetent patient

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ABSTRACT

Cryptococcus neoformans is generally observed with immunosuppressive conditions. Rarely, it may be seen in immunocompetent individuals and presented with non-specific conditions. We described an immunocompetent case of cryptococcal meningitis presented with multiple cerebral infarcts. Despite the late diagnosis and emergence of hydrocephalus during treatment, the patient was recovered without any sequelae. In immunocompetent patients, the conventional diagnostics tests may be negative because of the low fungal load. If it is available, the Biofire FilmArray meningitis panel has high sensitivity and specificity for diagnosis.

Introduction

Cryptococcus neoformans is an opportunistic fungus commonly seen in the environment. Cryptococcosis is an infection caused by the fungi *Cryptococcus neoformans* and *gattii*. The fungus is usually acquired by inhalation from the environment, and it may disseminate hematogenously to the central nervous system (CNS) [1]. Additionally, skin, eyes, bones, and soft tissue may be affected [2]. The immunosuppressive conditions are major risk factors for *C. neoformans* infections, such as advanced HIV/AIDS, idiopathic CD4+ lymphopenia, diabetes mellitus, organ transplantation, and prolonged corticosteroid usage [3]. Although the mechanism is not fully understood, CNS infection caused by *C. neoformans* may be rarely seen in immunocompetent individuals and the disease may occur with nonspecific symptoms that last for weeks [4]. In such cases, exposure to organisms with increased pathogenicity or undiagnosed immune deficiency may be the reason [5]. Despite the low frequency in immunocompetent patients, its mortality is high due to delayed or misdiagnosis [4].

We describe an immunocompetent man with cryptococcal meningitis (CM) who presented with multiple cerebral infarcts and cryptococcomas. During the therapy, although hydrocephaly emerged, the patient was recovered without sequelae.

Case report

In December 2016, a 59-year-old man who had suffered from headaches, slowdown in speech, inability to walk, and weakness was admitted to the hospital. On examination, his body temperature was 37.2 °C, with blood pressure 140/80 mmHg, a heart rate 84 beats/min, and respiratory rate 24 breaths/min. His neurological and fundoscopic examination were normal. Cranial MRI revealed bilateral cerebral-cerebellar multiple millimetric gliotic lesions and leptomeningeal enhancement. Based on the radiological appearance, infectious pathologies, lymphoma, or vasculitis were considered presumptively in the differential diagnosis (Fig. 1A). Lumbar puncture (LP) was performed, and the appearance of cerebrospinal fluid (CSF) was clear. The other CSF findings were as follows; the opening pressure (OP) of 19 cmH_2O, total leucocyte count (TLC) of 302/μL (polymorphonuclear 5%, lymphomononuclear 95 %), protein 113 mg/dL, glucose 30 mg/dL, and simultaneous blood glucose level 147 mg/dL. CSF lymphoma, paraneoplastic panel, *Mycobacterium tuberculosis* PCR and *Cryptococcus neoformans* with India ink were all negative. The acute ischemic cerebrovascular event was determined by cranial MR imaging and acetylsalicylic acid was ordered (Fig. 1B). The patient's clinical condition slightly improved day by day, but his headache did not remit.

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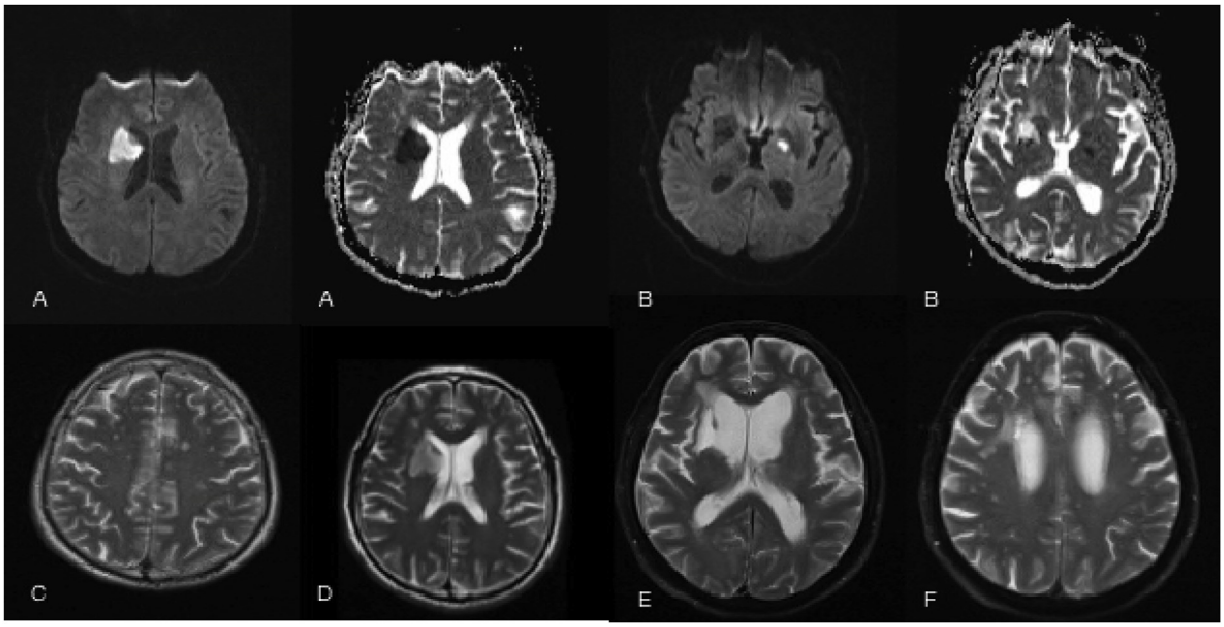

Fig. 1. (A) Diffusion-weighted imaging and ADC mapping show acute ischemic lesions in the right caudate nucleus (B) Diffusion-weighted imaging and ADC mapping shows acute ischemic lesions ingenue of the internal capsule on the left side (C) T2- weighted cranial MR imaging shows bilateral centrum semiovale and periventricular subcortical white matter hyperintensities, cryptococcomas (D) T2- weighted cranial MR imaging shows the chronic ischemic gliotic area (E) T2- weighted cranial MR imaging shows cerebral atrophy and hydrocephalus in the following time of the treatment (F) chronic lesions in the post-treatment period.

Eight months later, the patient presented with a slowdown in speech, sleepiness, and weakness. His neurological examination was unremarkable except for dysarthria and inability to walk. For the stroke etiology, we re-evaluated the cardiac source and large vessel occlusion, but we found all these sources in the normal range. Cerebral digital subtraction angiography was performed and left anterior cerebral artery segment A1, and right posterior cerebral artery segment P1 was reported as hypoplastic. Based on the acute multiple ischemic lesions in diffusion-weighted imaging and the clinical status of the patient, the vasculitis was presumptively diagnosed. Therefore, seven days of pulse steroid and one-day of cyclophosphamide treatments were given. The next day, fever was detected as 38.1 °C without headache and neck stiffness. We performed lumbar puncture (LP) which revealed an increased OP of 23 cmH_2O, with leucocyte count of 193 u L (polymorphonuclear 67 %, lymphomononuclear 32 %), protein 313 mg/dL, glucose 11 mg/dL, simultaneous blood glucose 101 mg/dL and therapeutic CSF drainage was performed due to high OP. Biofire Film Array Meningitis/Encephalitis panel was positive for *Cryptococcus neoformans/gattii*. On microscopic examination of CSF, cryptococcus-like encapsulated yeasts were demonstrated with India ink (Fig. 2).

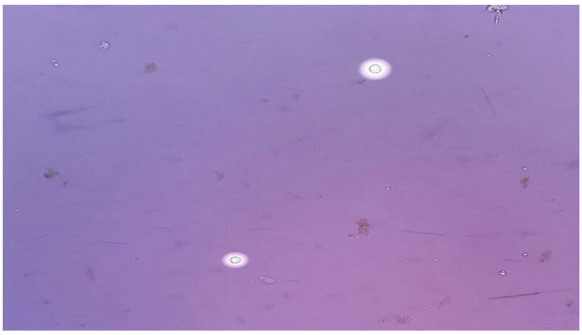

Fig. 2. India ink stain of CSF demonstrating encapsulated yeast-like fungus, *Cryptococcus neoformans.*

Liposomal amphotericin B (AmB) 5 mg/kg and fluconazole 800 mg/day were started immediately (flucytosine was not available in Turkey). Seven days later *Cryptococcus neoformans* was grown in CSF culture. A thorax tomography revealed no evidence of lung disease suggesting pulmonary cryptococcosis. The lesions in the previously performed cranial imaging were interpreted as cryptococcoma (Fig. 1C). The patient had not any known immune-suppressive disease or well-known risk factors for cryptococcosis. At the beginning of his hospitalization, a pulse steroid and cyclophosphamide were given with the suspicion of CNS vasculitis. HIV testing was negative and CD4 count was found in normal range for twice (1004-33% and 630-31%, respectively). On day 17 of treatment, LP was repeated and *C.neoformans/gattii* was positive in the Biofire FilmArray meningitis panel but yeast culture was negative. His clinical condition of the patient was improved partially after twenty days with consciousness, ability of walking, and speaking improving. At the end of six weeks of AmB treatment, it was withdrawn, and the patient was discharged with fluconazole for maintenance treatment.

Two weeks later, while the patient was taking 800 mg/day fluconazole, he presented with a deterioration of the general condition, confusion, aphasia. Cranial MRI was performed and the triventricular hydrocephaly was detected (Fig. 1E). Antiedema treatment was started and flucytosine was supplied. The antifungal treatment was started over again with flucytosine and AmB. Eight weeks later, induction treatment was stopped and switched to fluconazole. Fluconazole was given fifteen months totally for maintenance and consolidation therapy. His clinical condition was improved completely, and cranial imaging showed regression of previous lesions (Fig. 1F). After 8 months of finishing antifungal drugs, his condition was good and stable without any neurological findings or symptoms.

Discussion

Cryptococcal meningoencephalitis, which occurs with the entrance into the CNS of the fungus, is generally seen in immunocompromised patients, especially with HIV [6]. In Western

countries, among the cryptococcal CNS infections, only 20 % of cases were HIV negative [7]. In our case, we did not find any specific immunosuppressive condition, such as HIV, CD4+ lymphopenia, diabetes mellitus, but it was learned from the patient's history that he fed pigeons on his terrace. Since *C. neoformans* is typically found in soil, excreta of birds, especially pigeons, this may be assumed as a risk factor [8].

The immunocompromised patients with cryptococcus CNS infections usually have a shorter duration of symptoms before the hospital admission, probably because of having a higher burden of fungal organisms [9]. Unlike, the disease may be with the subacute onset and, symptoms may be subtle in immunocompetent patients [5]. Therefore, the diagnosis of CM may be challenging, and it is often misdiagnosed. Liao et al. showed that the time from onset symptoms to diagnosis is significantly longer in HIV-uninfected patients compared to HIV-infected patients ($p = 0.048$) [6]. The presentation of our immunocompetent patient was nonspecific, therefore at the beginning of his admission other reasons were investigated.

The nodular brain lesion known as cryptococcoma due to *Cryptococcus* is the least common form of CM and it is extremely rare in immunocompetent individuals compared to immunocompromised patients [10,11]. While some studies have indicated that cerebral cryptococcoma is more frequent in *C. gattii* meningitis than *C. neoformans*, others have shown contrary [12,13]. In a case series, all 5 cases misdiagnosed as tuberculoma or abscess before biopsy [13]. In our case, the lesions in cranial imaging were also supposed as tuberculoma or malignant nodules firstly.

Compared with other fungal pathogens, the cerebrovascular complications of CM, especially cerebral infarcts, are notably rare and usually occurred in patients with HIV [14]. In the early stages of CM, cerebral blood fluid is disturbed and, infarcts may be seen [15]. Chen et al. found the incidence of acute/subacute cerebral infarction as 19 % in HIV-negative patients, and multiple cerebral infarctions were the most common type (86 %) as in our case [14]. There are a limited number of case reports relating to cerebral infarcts in HIV-negative patients and, their therapeutic outcomes are quite poor [16]. Our patient was investigated for about 1 year due to cerebral infarcts. Despite the late diagnosis, the patient had a favorable outcome. The basic infectious diagnostic tests, including India ink, were done and none of them was positive. Shortly after corticosteroid treatment, the fever was detected, and the CSF panel was initially done. After its positivity, we applied India ink to CSF again and it was positive in this time. In the literature, longtime steroid treatment was defined as a risk factor for CM. However, in presented case, the specific symptoms appeared the day after corticosteroid treatment. The mechanism is not clear enough, but the pathogenicity or burden of the organism might increase with immunosuppressive treatment [5]. Thus, steroid treatment may have exacerbated the emergence of the full clinical presentation. This may also explain why India ink staining was negative previously.

Besides cerebral infarcts, hydrocephaly, which results from inflammatory exudates by CSF blockage, is a serious and more common cranial complication of CM [16]. The fungal polysaccharides may contribute that by blocking CSF outflow and disturbing CFS absorption [16]. Liao et al. have shown that hydrocephaly was related to poor outcomes in HIV-negative patients [6]. Hydrocephaly usually occurs as a late complication in untreated patients, and it was observed during a very early period of treatment in our case, probably because of delayed presentation.

CSF analysis is critical in immunocompetent and HIV-negative patients who have nonspecific symptoms [17]. The CSF may appear normal in the patients with cryptococcal meningitis. The fungal culture is the gold standard diagnostic method, but it can take at least 3 days. Therefore, the initiation of therapy is usually delayed [9,18,19]. India ink staining demonstrates encapsulated yeast on microscopic examination rapidly. Its sensitivity, however, which is approximately 80 % in patients with HIV, while <50 % in HIV-negative patients depending of the fungal burden [5,9,18]. Latex agglutination test has high sensitivity and specificity, but in the presence of low fungal burden, false-negative results may be seen [9]. A multiplex PCR assay (Biofire Film Array Meningitidis/Encephalitis Panel) detect pathogens more rapidly than other methods and it has high sensitivity and specificity (90 % and 97 %, respectively) [6]. In our case, shortly after pulse steroid treatment, *C.neoformans/gattii* was firstly detected by Biofire Film Array Meningitis/Encephalitis Panel. Rarely false-positive test results may be seen in the Biofire [19]. At the same time, the panel is expensive and does not distinguish *C. neoformans* and *C.gattii*. However, PCR provides rapid detection of *Cryptococcus* in CSF and, it may decrease time to initiation of targeted therapy, the length of stay and, cost [20]. Therefore, it is a useful test for immunocompetent individuals who have not been considered CM in areas with low prevalence.

In this case, despite the late diagnosis and various life-threating complications, fortunately, the patient was recovered without any sequel and is in remission for eight months since the end of the antifungal therapy.

Conclusion

CM is an opportunistic infection that generally occurred in immunocompromised, especially HIV positive patients. Besides, it may be seen rarely in immunocompetent individuals with nonspecific and more subtle symptoms. These patients may suffer from serious complications with high mortality. Therefore, *Cryptococcosis* should be considered in the differential diagnosis of immunocompetent patients, presenting with prolonged headache, cerebral infarct, and hydrocephalus in order not to delay diagnosis and treatment. Moreover, the fungal burden is lower in these groups of patients, and the sensitivity of India ink stain also decreases. If it is available, PCR is a very useful test that has high sensitivity and specificity.

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No competing financial interests exist.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Buket Erturk Sengel: Conceptualization, Resources, Writing-Original draft preparation.
Elif Tukenmez Tigen: Conceptualization, Resources, Review & Editing.
Rabia Can Sarinoglu: Methodology, Resources.
Ipek Midi: Writing - Review & Editing.
Nilgun Cerikcioglu: Methodology, Resources.
Zekaver Odabasi: Review & Editing, Supervision.

Ethical approval

No violation of patient privacy was done.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 2017;13:13–24.

[2] Mada P, Nowack B, Cady B, Joel Chandranesan AS. Disseminated cryptococcosis in an immunocompetent patient. BMJ Case Rep 2017;2017:.

[3] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010; (50):291–322.

[4] Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 2001;33:690–9.

[5] Poley M, Koubek R, Walsh L, McGillen B. Cryptococcal meningitis in an apparent immunocompetent patient. J Investig Med High Impact Case Rep 2019;7:2324709619834578.

[6] Liao CH, Chi CY, Wang YJ, Tseng SW, Chou CH, Ho CM, et al. Different presentations and outcomes between hiv-infected and hiv-uninfected patients with cryptococcal meningitis. J Microbiol Immunol Infect 2012;45:296–304.

[7] Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the us: 1997–2009. PLoS One 2013;8:e56269.

[8] Emmons CW. Saprophytic sources of cryptococcus neoformans associated with the pigeon (columba livia). Am J Hyg 1955;62:227–32.

[9] Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2016;30:179–206.

[10] Li Q, You C, Liu Q, Liu Y. Central nervous system cryptococcoma in immunocompetent patients: a short review illustrated by a new case. Acta Neurochir (Wien) 2010;152:129–36.

[11] Chen S, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D. Epidemiology and host- and variety-dependent characteristics of infection due to cryptococcus neoformans in Australia and New Zealand. Australasian cryptococcal study group. Clin Infect Dis 2000;31:499–508.

[12] Phillips P, Galanis E, MacDougall L, Chong MY, Balshaw R, Cook VJ, et al. Longitudinal clinical findings and outcome among patients with cryptococcus gattii infection in British Columbia. Clin Infect Dis 2015;60:1368–76.

[13] Uppar A, Raj ARP, Konar S, Kandregula S, Shukla D, Somanna S, et al. Intracranial cryptococcoma-clinicopathologic correlation and surgical outcome: a single-institution experience. World Neurosurg 2018;115:e349–59.

[14] Chen SF, Lu CH, Lui CC, Huang CR, Chuang YC, Tan TY, et al. Acute/subacute cerebral infarction (asci) in hiv-negative adults with cryptococcal meningoencephalitis (cm): a mri-based follow-up study and a clinical comparison to hiv-negative cm adults without asci. BMC Neurol 2011;11:12.

[15] Chang WN, Lu CH, Chang HW, Lui CC, Tsai NW, Huang CR, et al. Time course of cerebral hemodynamics in cryptococcal meningitis in hiv-negative adults. Eur J Neurol 2007;14:770–6.

[16] Chen YF, Wang DN, Chen ZT, Zhao ZH, Lin Y, Wang HY, et al. Risk factors associated with acute/subacute cerebral infarction in hiv-negative patients with cryptococcal meningitis. J Neurol Sci 2016;364:19–23.

[17] Hamdan N, Billon Grand R, Moreau J, Thines L. Cryptococcal meningitis in an immunocompetent patient with obstructive hydrocephalus: a case report. Neurochirurgie 2018;64:324–6.

[18] Dominic RS, Prashanth H, Shenoy S, Baliga S. Diagnostic value of latex agglutination in cryptococcal meningitis. J Lab Phys 2009;1:67–8.

[19] Tansarli GS, Chapin KC. Diagnostic test accuracy of the biofire® filmarray® meningitis/encephalitis panel: a systematic review and meta-analysis. Clin Microbiol Infect 2020;26:281–90.

[20] Rhein J, Bahr NC, Hemmert AC, Cloud JL, Bellamkonda S, Oswald C, et al. Diagnostic performance of a multiplex pcr assay for meningitis in an hiv-infected population in Uganda. Diagn Microbiol Infect Dis 2016;84:268–73.