Ain-Shams Journal of Anesthesiology

CASE REPORT Open Access

Cryptococcus Neoformans meningoencephalitis in an HIV-seronegative patient: a case report

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Background

Cryptococcal meningoencephalitis is an important opportunistic infection that usually affects immunocompromised patients. Usually seen in HIV (human immune deficiency virus)-seropositive patients, *Cryptococcus neoformans* may also be seen in patients who receive immune-suppressing glucocorticoid treatment, undergo solid organ transplant, have cancer, especially hematologic malignancies, and liver failure (Messina et al. 2017). However, in rare cases, Cryptococcal meningoencephalitis can be seen in suspected immunocompetent patients as well.

Case presentation

A 55-year-old male was admitted to the emergency department of Istanbul Medipol University hospital with difficulty in walking, talking, and decreased attention to his surroundings. He reported having similar symptoms for the last 2 months and was admitted to various hospitals and was diagnosed. A cranial MRI (magnetic resonance imaging) performed revealed multiple infarcts in sub-millimetric range. Due to deterioration of his consciousness, he was admitted to the ICU (intensive care unit). He did not report any predisposing condition and was negative for HIV antibodies. He was performed an LP (lumbar puncture), and an analysis of CSF (cerebrospinal fluid) revealed a WBC (white blood cell) count of 107/mm^3, glucose of 0.1 mg/dL (*N* 40–70), and CSF total protein of 116.9 mg/dL (*N* 10–45). Antituberculosis regimen comprising isoniazid, rifampin, ethambutol, and pyrazinamide was initiated empirically concomitant with prednisolone since a tuberculous meningoencephalitis was suspected. The following day, his neurological status worsened; he developed anisocoria and was intubated. Bacterial cultures and a multiplex PCR (polymerase chain reaction) for possible viral and bacterial, including tuberculosis, remained negative. Systemic evaluation was otherwise unremarkable. On the third day of ICU hospitalization, cranial MRI and LP were repeated. Diffusion MRI showed symmetric, bilateral diffuse cytotoxic edema on cerebral cortex of sylvian and interhemispheric fissure and subtemporal region and pulvinar. There was triventricular hydrocephaly but no hemorrhage. CSF showed similar cell count glucose and protein levels compared to initial evaluation and was further tested for brucellosis, syphilis, HIV infection, and other possible viral causes of meningitis and encephalitis. Repeated bacterial cultures were negative; however, fungal cultures grew *Cryptococcus neoformans*. Cytopathological examination of cerebrospinal fluid also confirmed presence of fungi. On the fourth day of ICU hospitalization, antituberculosis treatment and steroids were stopped and a combination of amphotericin B lipid complex 5 mg/kg iv and fluconazole 1 × 800 mg iv was commenced. Despite antifungal treatment, patient developed septic shock and died on the tenth day of hospitalization.

Discussion

The fungal infections of central nervous system carries a higher risk of morbidity and mortality compared to other infections and, therefore, require prompt diagnosis and appropriate medical and surgical management to optimize their outcomes (Raman Sharma 2010). Cryptococcus meningoencephalitis is an important opportunistic infection that usually affects patients with immunocompromised states, including AIDS, malignancy, and immunosuppressive therapy. However, an increasing number of patients with cryptococcosis in apparently immunocompetent persons are also

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reported from different parts of the world. Pyrgos et al. reported that 21.6% of their patients with Cryptococcus meningoencephalitis were HIV-negative (Pyrgos et al. 2013).

The clinical picture of cryptococcosis may be different in immunocompetent or HIV-seronegative patients. Some patients have symptoms for months before a diagnosis is made. We believe that the fatality of case may be related to delayed diagnosis and treatment.

Most immunocompetent patients have a subacute meningoencephalitis with only 50% presenting with fever (Qu et al. 2017). Headache, paresthesia, personality changes, and memory loss for the last 2–4 weeks are the most common symptoms. Our patient had nonspecific symptoms including fever and dyspnea for 2 months prior to diagnosis. During the second month of his symptoms, he reported difficulty in walking, talking, and a decreased attention to his surroundings.

Cryptococcosis is usually seen in patients with HIV infection, solid organ transplants, cancers, especially hematologic malignancies, liver failure, and patient receiving glucocorticoid treatments. Use of tyrosine kinase inhibitors, ibrutinib, and anti-granulocyte-macrophage colony stimulating factor (anti-GM-CSF) can depress the immune system as well (Rosen et al. 2013). In a multicentered retrospective study, 30% of 157 HIV-negative patients with Cryptococcus CNS involvement were reported to have none of the known immunosuppressive conditions (Pappas et al. 2001). And similarly like our case report, we did not find any predisposing factors for immune depression.

Tracking intracranial pressure (ICP) is crucial for the management of cryptococcal meningoencephalitis. If the ICP is ≥ 25 cm H_2O and increased ICP symptoms are present, CSF drainage should be done (Graybill et al. 2000). An external ventricular drainage system was also applied to our patient since MRI showed triventricular hydrocephaly.

The diagnosis of cryptococcus meningoencephalitis is made by the organism being present in the CSF. Around 90% of HIV-negative patients have positive cultures for *Cryptococcus*. Optimum amount of CSF should be around 3–5 mL for culture, and 3–5 days may be required for growth (Saag et al. 1992). On the first day in the ICU, CSF was obtained from our patient and was later advised to check for cultures of fungal or opportunistic infections. The results were positive for *Cryptococcus neoformans*.

Our patient was treated with a combination of amphotericin B lipid complex (AmBisome 5 mg/kg) and fluconazole (800 mg daily, 12 mg/kg IV) in reference to the Infectious Diseases Society of America 2010 Guidelines (Perfect et al. 2010). The treatment could only be administered for 5 days before the patient's death. If diagnosis was made earlier starting from the symptoms presenting 2 months prior, the patient's odds of survival might have been increased.

Conclusion

Patients with nonspecific signs and symptoms must go through all differential diagnosing for the possible causes. In hospitals with many patients, this might not be possible, and this attention to detail might be skipped. Instead of sending the patients home after they have stabilized, they should be admitted to have a thorough physical examination and laboratory evaluation with frequent checks until normalized. Early diagnosis and start of treatment are the keys, in many instances, to recovery. As important as the classic predisposing factors are, we must also keep in mind that illnesses may arise without these factors. In our case of an HIV-negative patient with no predisposing factors, the early diagnosis and start of treatment might have controlled the disease.

Abbreviations

HIV: Human immune deficiency virus; MRI: Magnetic resonance imaging; ICU: Intensive care unit; LP: Lumbar puncture; CSF: Cerebrospinal fluid; WBC: White blood cell; PCR: Polymerase chain reaction; ICP: Intracranial pressure

Acknowledgements

Not applicable

Authors' contributions

DK: Writing, literature scanning. CE: literature scanning, analysis or interpretation. EAY: English translation. PK: Design and concept. The author(s) read and approved the final manuscript.

Funding

The authors received no financial support for the research and/or authorship of this article.

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Consent was obtained from the patient's legal representative and there was no objection to the case presentation.

Competing interests

The authors declare that they have no competing interests.

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Received: 4 October 2019 Accepted: 23 March 2020
Published online: 16 April 2020

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