Candida Meningitis in an Immunocompetent Patient Detected Through (1\(\beta\))-D-glucan

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Case Report

Candida meningitis in an immunocompetent patient detected through (1→3)-beta-D-glucan

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ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 23 August 2016
Accepted 24 August 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Intravenous drug abuse
Candida meningitis
(1→3)-beta-D-glucan
Fungal cerebrospinal fluid

SUMMARY

A 44-year-old female presented with a 3-month history of headache, dizziness, nausea, and vomiting. Her past medical history was significant for hypertension and intravenous drug abuse (IVDA), and chronic hepatitis C. The symptoms had started with daily, intermittent headaches for roughly 3 months before her admission. The headaches could be exacerbated by light or screening, and ibuprofen partially relieved the pain. About a month following the onset of headaches, she developed gait instability. She ultimately decided to come to the hospital after developing severe nausea, vomiting, and dizziness. On further questioning, she denied any fever, chills, incontinence, sputum production, hemoptysis, or cough. The patient had a 26-year history of IVDA. A urine drug screen performed on admission was positive for bunprenone, benzodiazepine, and opiates.

On arrival, the patient was afibrile and had a blood pressure (BP) of 126/92 mmHg and heart rate of 111 bpm. Laboratory test results, including the complete blood profile and basic metabolic profile, were grossly normal. A physical examination demonstrated photophobia, but was otherwise unremarkable. Computed tomography (CT) of the brain without contrast showed a disproportionate prominence of the ventricles relative to the cortical sulci, raising the question of possible normal pressure hydrocephalus; magnetic resonance imaging (MRI) of the brain revealed similar findings. A chest X-ray showed no focal infiltrates, and HIV antibody testing, as well as PCR testing, was negative. The patient was admitted with a suspicion of normal pressure hydrocephalus.

After admission, the patient spiked episodic fevers as high as 38.8 °C. Blood and urine cultures were drawn. The following day, the patient continued to have episodic fever and also became hypertensive with a BP of 190/90 mmHg. A subsequent lumbar puncture demonstrated an opening pressure of 310 mmHg, and cerebrospinal fluid (CSF) studies showed glucose of 7 mg/dL, protein of 357 mg/dL, 2 × 10⁶ red blood cells/L, and 203 × 10⁶ white blood cells/L, with >50% neutrophils. Gram staining did not reveal any organisms and CSF cultures were initiated. CSF flow cytometry showed no evidence of acute leukemia or lymphoma. Additional CSF assays evaluating possible tuberculosis, syphilis, Epstein–Barr virus, cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, and Cryptococcus neoformans were negative. Furthermore, tests for blastomycosis and histoplasmosis were also negative. The blood cultures drawn on admission showed no growth in 4 days. She was then started on empiric vancomycin and piperacillin/tazobactam for possible bacterial meningitis.

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http://dx.doi.org/10.1016/j.ijid.2016.08.020
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On hospital day 4, the patient continued to experience episodic fever and uncontrolled hypertension. The patient also became confused and would regularly only be oriented to person and/or place. An ophthalmological examination revealed papilledema. Multiple escalations of her blood pressure regimen failed to achieve control. Ultimately, she was given an anti-hypertensive regimen consisting of metoprolol 50 mg, clonidine 0.1 mg twice daily, clonidine 0.1 mg as needed, lisinopril 20 mg daily, and hydralazine 5 mg every 6 hours as needed; her blood pressure continued to measure between 154/104 and 224/136 mmHg.

Repeat serology and CSF studies for possible organisms continued to be negative. Gram staining and India ink staining did not show any organisms. Repeat CSF cultures, including bacterial, acid-fast bacilli, and fungal, were started. Serum (1→3)-β-D-glucan (BDG) was low at 48 pg/ml.

As no organism could be identified, the patient continued to receive empiric treatment for bacterial meningitis and supportive care. Fungal meningitis remained high on the differential given the chronic presentation and findings of hydrocephalus. However, due to the morbidity associated with amphotericin B treatment, empiric antifungal treatment was not started. The patient remained hypertensive and experienced episodic fever, requiring therapeutic large-volume lumbar punctures every 3–4 days. Other studies, including West Nile virus serum and CSF PCR, as well as Lyme disease serology, were negative. Repeat imaging demonstrated only small focal enhancement within the midbrain, which could not be sampled.

On her 16th day in the hospital, the fungal culture from the second lumbar puncture performed on hospital day 7 grew fewer than five colonies of Candida albicans. While it was encouraging to obtain a potential causative agent, there was concern over possible contamination given the small yield. To confirm the diagnosis, BDG testing of saved CSF from the positive culture showed levels >500 pg/ml. Repeat serum BDG testing was still negative. The patient began treatment with liposomal amphotericin B; fluconazole was held due to low blood counts. After starting treatment, the patient’s blood pressure and mentation began to improve. Follow-up ophthalmological examinations demonstrated resolving papilledema and she was consistently afebrile. After 14 days of liposomal amphotericin B treatment, the patient was discharged home on an indefinite course of fluconazole 800 mg.

In 2012, several patients developed CNS complications due to the contamination of methylprednisolone epidural injections with C. albicans. From this outbreak, researchers evaluated the utility of the BDG assay to improve upon the diagnostic limitations of traditional culture methods. BDG is a fungal cell wall component highly enriched in C. albicans, Aspergillus, and other fungal species. Notably, BDG is not highly expressed in Cryptococcus fungi. The test was initially developed for blood sampling, with levels <60 pg/ml negative, 60–80 pg/ml indeterminate, and >80 pg/ml positive. According to Viracor, a BDG assay manufacturer, there is no determined reference range for CSF. Despite this fact, physicians have evaluated the utility of BDG testing of CSF with impressive results.

One study demonstrated that a cut-off level of 138 pg/ml revealed Candida meningitis with a sensitivity of 98% and specificity of 100%, whereas another showed that a cut-off level as low as 66 pg/ml had 91% sensitivity and 92% specificity in the setting of probable meningitis. Others have reported that a CSF BDG cut-off value of 110 pg/ml can diagnose CNS fungal infections with a sensitivity of 100% and specificity of 96%. Furthermore, another study found BDG levels to be useful for evaluating the response to therapy, as physicians monitored serial CSF BDG measurements in patients with fungal meningitis receiving treatment until they eventually fell below 31 pg/ml.

In the current case, only one out of four fungal CSF cultures grew C. albicans, and only sparsely. This is consistent with previous observations and demonstrates the poor sensitivity of this diagnostic approach. Furthermore, serum BDG testing was consistently negative, in agreement with prior reports on serum BDG levels in CNS fungal infections. On the other hand, BDG testing of the CSF revealed levels >500 pg/ml, which is well above reported cut-off values for this assay.

This case report demonstrates a rare complication of IVDA and supports CSF BDG testing as a viable option for the diagnosis of Candida meningitis.

Funding: There was no declared funding source for this report.

Ethical approval: No identifying material was used, therefore approval was not required.

Conflict of interest: The authors declare no conflicts of interest, financial or otherwise.

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