

Co-infection with Cryptococcal Meningitis and Japanese Encephalitis in an Immunocompetent Patient: A Case Report

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ABSTRACT

Cryptococcal meningitis is a severe infection in both immunocompetent and immunosuppressed hosts. This report is an unusual case of co-infection with cryptococcal meningitis and Japanese encephalitis in a seronegative human immunodeficiency virus patient. A 51-year-old human immunodeficiency virus-negative patient presented with high-grade fever, nausea, vomiting, and later on, behavioral changes. A lumbar puncture was performed and cerebrospinal fluid revealed the presence of *Cryptococcus* and Japanese encephalitis virus. Treatment commenced with intravenous amphotericin B and flucytosine. Her condition initially improved but later on deteriorated due to bacteremia (MRSA-mecA gene positive) and septic shock which resulted in the patient's demise. The occurrence of this co-infection in the absence of HIV infection is rare and there was no documented case up to this date.

Keywords: *Co-infection, Cryptococcal Meningitis, Japanese Encephalitis*

BACKGROUND

Cryptococcal meningitis (CM) is considered to be the most common central nervous system infection (CNSI) among patients with severe immunodeficiency syndrome secondary to human immune deficiency virus with an incidence of 0.09 per 100,000 population in the Philippines¹ but this condition could also be present in immunocompetent hosts, with no incidence recorded in the Philippines. In the United States, cryptococcal meningitis occurs in immunocompetent patients with an incidence of 0.4 to 1.3 cases per 100,000 people. Co-infection with other CNS infections is relatively common especially with tuberculous meningitis and neurosyphilis² however, there was no reported case of co-infection with cryptococcal meningitis and Japanese encephalitis (JC). In the Philippines, JC cases comprise around 15% of all encephalitis cases last 2016 in Regions I and II³ (Department of Health, 2019).

CASE PRESENTATION

A 51-year-old female was admitted to the emergency room with a chief complaint of change in behavior. The patient was admitted a week before in a local hospital due to intermittent severe diffuse headache associated with high-grade fever, nausea, and vomiting. She was managed as a case of dengue fever then four days later, she was noted to be uncooperative, does not respond to family members, and restless. She was then diagnosed to have dengue encephalitis and she was transferred to our institution for further evaluation and management. She had no medical or surgical history, pertinent sexual history, and history of drug or alcohol abuse. The patient came from Nueva Vizcaya Municipality, Cagayan Valley, Philippines and she reportedly had exposure to domesticated chickens.

Vital signs included a body temperature of 36.5 °C, respiration of 20 breaths/min, heart rate at 98 beats/min, blood pressure of 120/80 mmHg, and oxygen saturation of 98% on ambient air. Physical examination showed akinetic mutism, no

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frontal release signs, no craniopathies, no weakness, nuchal rigidity, and positive Kernig's and Brudzinkli's signs.

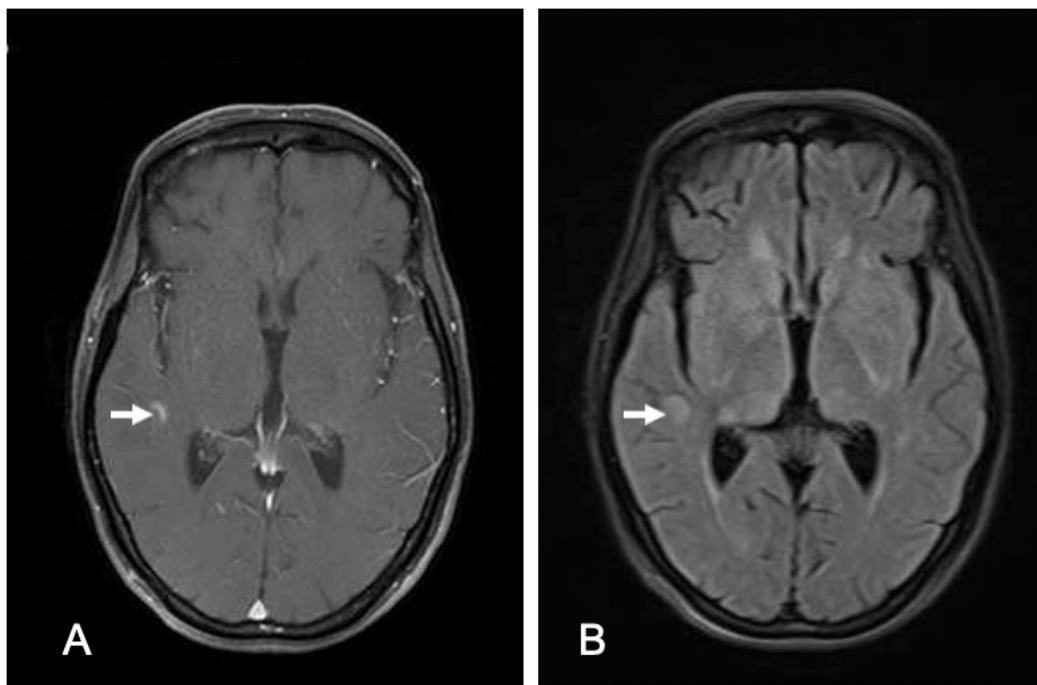
Laboratory test results are as follows: a normal leukocyte count of $6.7/\text{mm}^3$ (reference range $5.0\text{--}10.0/\text{mm}^3$), with neutrophilic predominance of 79% (reference range 50-70%) and a low lymphocytes at 16% (reference range 20-40%), high c-reactive protein 8.05 mg/L (reference range 0-5 mg/L), Erythrocyte Sedimentation Rate showed 58 mm/hr (reference range 0-30 mm/h). Serum sodium and potassium, as well as creatinine, were unremarkable. The biochemistry testing on the liver was normal. A lumbar puncture (LP) showed an elevated opening pressure of 23 cmH₂O (1 cmH₂O=0.1 kPa).

Cerebrospinal fluid (CSF) analysis was revealed to be acellular. The glucose ratio was decreased at 0.25 mg/dL (reference range 40-60 mg/dL) and protein level was elevated at 196 mg/dL (reference range 15-45 mg/dL). CSF Polymerase chain reaction (PCR) for Herpes simplex, Epstein Barr virus, Varicella,

and Cytomegalovirus were negative. CSF Acid-fast staining and Gene Xpert were negative. Cryptococcal Antigen Latex Agglutination System (CALAS) and CSF IgM-capture enzyme-linked immunosorbent assay (ELISA) for Japanese encephalitis showed confirmatory results while serum Japan Encephalitis ELISA tested negative. The patient was seronegative for human immunodeficiency virus (HIV). Electroencephalogram (EEG) revealed an intermittent generalized slowing towards the middle of the recording, suggestive of a cortical-subcortical dysfunction. Cranial Magnetic resonance imaging (MRI) with intravenous contrast showed nodular hyperintensity on the right temporal area in T2 Flair and peripheral nodular enhancement in T1 Contrast Gadolinium (Gd) (Figure 1).

The patient was managed with a meningitic dose of Ceftriaxone for seven days and was later on shifted to liposomal amphotericin B and flucytosine (5-fluorocytosine) as induction therapy. Her condition improved in the first week of treatment as evidenced by increasing verbal

Figure 1. A. On T2 Flair revealed a nodular hyper-intensity on the right temporal area
B. T1 C+ Gd showed a peripheral nodular enhancement.



output. On the 14th day of antifungal treatment, the patient was intubated due to decrease sensorium, desaturations, with concomitant hypotension. During infusion of amphotericin, she had phlebitis on the left arm.

On blood culture, methicillin-resistant *Staphylococcus aureus*- *mecA* gene positive was noted on blood A and B subsequently, intravenous antibiotics were immediately started. Unfortunately, she died of respiratory failure and septic shock after a month of admission.

DISCUSSION

Cryptococcal meningitis is a severe infection in both immunocompetent and immunosuppressed hosts. This disease is considered to be an opportunistic and lethal condition, especially in patients with HIV/AIDS, transplant recipients, and autoimmune diseases. The reported prevalence of Cryptococci infection is persistently common in males in both seronegative and seropositive HIV patients.⁴ Cryptococcus species are frequently present in territories associated with wood debris, soil, and bird excreta (usually pigeon droppings and chicken manure).⁵ The estimated mortality rate of cryptococcal meningitis in a recent study conducted in Wuhan, China was 35% (36/103)⁶.

On the other hand, Japanese encephalitis is a vector-borne disease transmitted by *Culex* mosquitoes and predominantly occurs in Southern and Eastern Asia. In the Philippines, cases were recorded since 2017 in Nueva Vizcaya, Cagayan Valley.⁷ The classic manifestation of Japanese encephalitis includes fever, seizure, change in behavior, tremor, dull flat mask-like facies with wide unblinking eyes, cogwheel rigidity, and generalized hypertonia. The mortality index may reach up to 30% and approximately half of the survivors experience severe neurologic residuals.⁸ Similarly, a systematic review regarding Japanese

encephalitis reported a 20-30% mortality rate, and around 30-50% of survivors have neurologic sequelae.⁹

Currently, there is no written documentation regarding co-infection of cryptococcal meningitis and Japanese encephalitis. The sensitivity and specificity of CALAS in detecting cryptococcal meningitis in CSF were 98-100% (10). Using IgM-captured ELISA in detecting Japanese encephalitis offers sensitivity and specificity of 98% and 99% respectively. Among these mentioned microorganisms, there was no recorded cross-reactivity during testing.

Patients may develop MRSA bacteremia during or shortly after the management of CM; the possible portal of entry is the peripheral venous cannula used to administer intravenous fluids and amphotericin B (11).

CONCLUSION

The coexistence of two lethal types of central nervous system infection is indicative of a poorer outcome based on the reported individual mortality rates of Japanese encephalitis and cryptococcal meningitis. Here we present a case of an immunocompetent host with a dual infective pathology which resulted in an unfavorable outcome. Further investigations are needed to identify a correlation between co-infectivity and treatment strategies.

A high level of suspicion regarding co-infection should be entertained if history involves the area of exposure and the working environment.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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All procedures and management done to the patient were included in his public insurance policy.

CONFLICT OF INTEREST

The authors declare that the case report was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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