Immunocompetent patient with cerebral cryptococcosis: case report

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Abstract

A 14-year-old female, presenting sudden and progressive holocraneal headache along with incoercible vomiting arrived to emergency room. Acute confusional state and meningoencephalitis syndrome were identified. Brain computed tomography-scan with normal results was performed. Lumbar puncture with crystal-clear cerebrospinal fluid was obtained: low glucose, elevated proteins and cell-count of 15/mm. China-ink and *Cryptococcus neoformans* culture both positive. Viral, lupus-anticoagulant, and HIV tests negative. Fluconazole 200 mg/kg/day, amphotericin-B 0.7 mg/kg/day, dexamethasone 1 mg/kg/day were prescribed. 48-h later evolved to cerebral edema, multiple-organ-failure and death. Hereby we present a *Cryptococcus* spp. infection case report, addressing the public health challenge and vulnerability of immunocompromised patients in Mexico.

KEY WORDS: Headache. Cerebral cryptococcosis. *Cryptococcus gattii*. *Cryptococcus neoformans*. Multiple organ failure. Immunocompetent. Meningoencephalic syndrome.

Introduction

Cryptococcosis is an opportunistic fungal disease caused by a globally-distributed yeast-like, encapsulated fungus¹. There are two pathogenic varieties in the human being: *Cryptococcus neoformans* var. *neoformans*, which causes the majority of infections in immunocompromised patients, and var. *gattii*, which affects immunocompetent individuals and exists in both tropical and subtropical areas²⁻⁴.

Cryptococcosis diagnosis is based on a detailed patient history, since symptoms depend on the area compromised in the central nervous system (CNS). In case of clinical suspicion after cytological, cytochemical and cerebrospinal fluid (CSF) staining tests, an enzyme-linked immunosorbent assay (ELISA) or a latex agglutination test should be carried out; when both

these are negative, the CSF culture results should be awaited⁵. Untreated meningitis by *Cryptococcus* spp. is fatal, while 60-70% of patients without AIDS who are treated have good prognosis^{6,7}.

The present case exemplifies the importance of *Cryptococcus* spp. infection in immunocompetent patients in our country, since in spite of medical management and standardized treatment, the patient had organ dysfunction and died.

Case presentation

This is the case of a 14-year-old female patient, resident of an urban area in Morelia, Michoacán, who had a low socioeconomic status and poor hygienic-dietary habits. She had complied with her vaccination schedule. She had no relevant personal, family or

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psychiatric history. Her condition had started in December 2014 with holocranial headache of sudden and progressive onset, which was oppressive, constant, with no rhythm or irradiation, 8/10 intensity in the verbal rating scale for pain (VRSP), and was unsuccessfully treated with acetaminophen, with one-month evolution.

At her admission to the emergency department on January 2014, the patient presented with constant holocranial headache of VRSP 9/10 in intensity, accompanied by nausea, vomiting and tonic-clonic seizures. Her vital signs were: heart rate, 110 beats per minute; respiratory rate, 25 breaths per minute, blood pressure, 100/75 mmHg, moderate dehydration, acute confusional syndrome with psychomotor agitation state and meningoencephalic syndrome. Laboratory tests at admission showed blood count with leukocytosis and normal blood chemistry and coagulation times; normal plain and contrast cranial computed tomography (CT) (Fig. 1). Empirical treatment was started with ceftriaxone, 1 g every 12 h by intravenous (IV) route, and vancomycin, 15 mg/kg IV every 12 h. Lumbar puncture for CSF showed 80 mmH₂O opening pressure; cytochemistry: xanthochromic color; transparent appearance; protein, 78 mg/dL; glucose, 14 mg/dL; cellularity, 15/mm; lymphocytes, 20%; polymorphonuclear cells, 76% and monocytes, 4%. *Cryptococcus neoformans* was observed with India ink (Fig. 2). Therefore, treatment was started at 48 h with fluconazole 200 mg/kg/day, amphotericin B 0.7 mg/kg/day and dexamethasone 2 mg/kg/day. The TORCH, VDRL, B19 parvovirus, Epstein-Barr virus, anti-dsDNA (256 IU/mL), ANA (1:40) and HIV tests were negative. The CSF culture showed development of *C. neoformans* (sensitive to flucytosine ≤ 1 minimum inhibitory concentration [MIC] amphotericin B = 1 MIC and fluconazole = 2 MIC).

In spite of the treatment, the patient evolved with severe cerebral edema and neurological deterioration (Fig. 3), she developed multiple organ failure and died 3 days later. No autopsy was practiced.

Discussion

Cerebral cryptococcosis in immunocompetent patients is rare, and only a few have been reported in the world cases⁸. The variety of *Cryptococcus* is determinant for infection in immunocompetent patients but, unfortunately, in most cases the variety is not known, since the performance of polymerase chain reaction and ELISA is not common practice. Currently,

Figure 1. Normal plain cranial tomography at emergency department admission.

Figure 2. Bacterioscopic examination with India ink, where *Cryptococcus neoformans* are observed (arrows). A: 10x. B: 40x.

chronic undernourishment is an important element in developing countries⁹; coexistence with poultry and pigeons is the most common risk factor. The risk factors identified in our patient were being resident of a marginalized urban area and coexistence with poultry. In Mexico, *C. neoformans* has been isolated in 20.7% of pigeon excrements collected in urban areas, and to a lesser proportion in vegetables, fruits and other birds' excrements¹⁰.

Most common clinical presentation is pulmonary, wherefrom it can spread by the hematogenous route to the CNS and cause meningoencephalitis¹¹⁻¹³. When travelling through the blood stream, the fungus inhibits the host's immune response and the production of tumor necrosis factor, among others^{14,15}. Our patient had no data consistent with prior pulmonary infection;

Figure 3. Plain cranial tomography showing severe cerebral edema.

cases of asymptomatic pulmonary cryptococcosis and pulmonary infection-secondary meningoencephalitis have been reported without pulmonary clinical or radiologic data and, in these cases, the pulmonary infection is controlled by granulomas that disappear after weeks or months^{16,17}. Cryptococcosis presentation in the CNS can be as cysts in the cerebral cortex with granulomatous meningeal reaction, or granulomas in the white matter known as cryptococcomas^{18,19}, which were not detected in our patient; her medical condition precluded the performance of magnetic resonance.

Cryptococcosis clinical manifestations appear at 1 to 2 weeks after exposure to spores in bird feces, plants (eucalypts) and animals (e.g., koalas)²⁰. Immunocompetent patients can develop symptoms after months or with slow progression. Initial symptoms include progressive holocranial headache, general deterioration and fever that only occurs in 50% of cases. As for neurological symptoms, higher prevalence and more intensity have been observed in immunocompetent patients, with local or general manifestations depending on the area affected by the yeasts²¹⁻²³. In our patient, the first CT was normal; however, it has been documented that CT can be normal or show cryptococcomas in 38-58%, cerebral edema, hydrocephaly or meningeal enhancement. Magnetic resonance is more sensitive to detect nodules within the cerebral parenchyma; meninges, basal ganglia and mesencephalon are abnormal in 40% of patients with the infection typical presentation^{23,24}. CSF cytochemical examination shows lymphocytic pleocytosis, hyperproteinorachia and hypoglycorrhachia, and the Indian ink test is

positive in 50% of patients without AIDS²⁵. The most widely used diagnostic method is *Cryptococcus* culture (90% sensitivity); however, latex agglutination has been reported to be the diagnostic test with the highest sensitivity and specificity with titers higher than 1:2048²⁶.

Regardless of patient neurological and immune status, the recommended treatment for cerebral cryptococcosis is with amphotericin B (0.7-1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day by oral route, in four divided doses) for at least 4 weeks, and when there are complications (intracranial hypertension, among others), 6 weeks of induction therapy are recommended to subsequently start consolidation with fluconazole (400 mg/day) for 8 weeks. After induction and consolidation therapy, maintenance therapy is established with fluconazole, at 200 mg per day for 6-12 months²⁷.

Prognosis is poor in immunodepressed and immunocompetent patients without treatment; with treatment, worldwide-reported mortality in immunocompetent patients is 27%, and in immunodepressed subjects it is 32%^{28,29}. Cerebral cryptococcosis in immunocompetent patients is infrequent; however, it can have a fatal evolution in spite of currently recommended antimicrobial treatment.

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