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Case Report

Fatal neurocryptococcosis in a Colombian underage patient

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Abstract

Cryptococcosis is a life-threatening mycosis reported mainly in human adults with low frequency in children. High mortality rates may occur in cases with late diagnosis therefore, a timely suspicion of this pathology is important. *Cryptococcus gattii* is the less prevalent species complex predominantly isolated from apparently normal hosts. We report a fatal case of neurocryptococcosis in a Colombian minor without known risk factors, in Barranquilla, Colombia. The patient was hospitalized for neurological assessment with a recent history of intense headache, vomiting, anorexia, loss of consciousness, drowsiness, inability to recognize family members, disorientation, aphasia and anxiety. Despite initiating antifungal treatment after isolation of the fungus from cerebrospinal fluid (CSF), the patient died early due to his deteriorated condition.

Key words: neurocryptococcosis; *Cryptococcus gattii;* VGII; underage; minor; Colombia.

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Introduction

Cryptococcosis has evolved as a life-threatening fungal disease over the last century affecting man and other vertebrates. It is primarily observed in immunocompromised adults; infections in children are uncommon according to worldwide published English literature. The main etiological agents of this mycosis are two species complexes: *Cryptococcus neoformans* the most prevalent worldwide in immunocompromised patients and *Cryptococcus gattii* considered more virulent than its sibling and prevalent mostly in immunocompetent or apparently normal hosts. Both species complexes can be differentiated into four serotypes (A and D or B and C), several hybrids (AD, AB, and BD) and nine molecular types (VNI-IV, VNB, VGI-IV) [1].

Regarding cases of cryptococcosis in underage patients in South America, Brazilian children have been diagnosed with this mycosis in northern as well as in southern regions of the country, occurring more frequently in middle childhood (6-12 years). It is noteworthy that with respect to etiology, cases from Northern Brazil occurred mostly in patients without underlying conditions and were mostly associated to *C. gattii* in contrast to southern cases were patients had different underlying factors and were predominantly related to *C. neoformans* [2]. Lizarazo *et al*. (2014) published a report about cryptococcosis in Colombian children (1993-2010), finding 41 underage patients, with a prevalence of 2.6% and a mean annual incidence of 0.017 per 10^5 children; the average age in this cohort was 8.4 years and 58.5% were males; no risk factors were identified in 46.3% of them. Furthermore, in the department of Norte de Santander, a geographical region in Northeastern Colombia, the incidence was unexpectedly higher (0.122 per 10^5 children) [3]. Escandón *et al.* updated the data of this mycosis in Colombia (1997-2016) and reported 49 cases of cryptococcosis in minors (<16 years) which stands for a prevalence of 2.5%. It is important to highlight that these patients were mostly affected by *C. gattii*, an interesting finding that requires further study considering that cryptococcosis is an unusual event in this population [4]. Our aim is to present a fatal case of neurocryptococcosis by *C. gattii* in a Colombian underage patient without any known risk factors.

Case Report

A 10-year old male from an indigenous community in the northeastern peninsula of Colombia and without remarkable previous medical history, was referred from a basic health care institution to a higher-level health care facility, for neurological assessment to rule out encephalitis. On admission, the patient had a history of

headache and malaise for 21 days and after consulting a basic health care service, he was treated with conventional analgesic drugs- dipyrone/diclofenac plus dexamethasone (dosage and duration of treatment not recorded), with slight improvement of headache. The patient was also treated with diazepam (dosage and duration of treatment not recorded) due to disorientation, anxiety and aphasia with some improvement of his anxious condition. Symptomatology persisted and was aggravated with throbbing headache (9/10) associated with projectile vomiting and anorexia; seven days prior to the admission, the patient presented fetid liquid yellow stools (6 per day), loss of consciousness, drowsiness and inability to recognize family members. Due to the clinical findings, a remission to a higher complexity health facility was made for proper diagnosis, treatment and follow-up.

On admission the patient was in fair general condition: slightly tachypneic, afebrile, hydrated and tolerating well ambient air; physical exam was within normal, without apparent neurological deficit and muscle strength was preserved. He was sent to the pediatric ICU with presumptive encephalitis; neurological assessment was requested as well as routine diagnostic tests regarding chemistry (renal and hepatic profile, electrolytes), hematologic and serologic profiles including HIV and coagulation tests. Basic laboratory tests regarding clinical chemistry, hematology and electrolytes indicated on day 2, leukocytosis (16,500/mm^3) with neutrophilia (13,700/mm^3) and monocytosis (1,200/mm^3); hemoglobin (12.2 g/dL), hematocrit (33.9%) and corpuscular parameters were consistent with microcytic and hypochromic anemia; sodium, potassium and chlorine were slightly reduced (134, 4.5 and 96.1 mEq/L, respectively). Additionally, CT scan and chest X-rays were performed and reported normal; a brain MRI revealed demyelinating lesions suggesting hypoxic origin, without inflammatory activity. HIV 1+2 were negative; blood culture was negative for common germs.

The patient had two lumbar punctures within nine-days interval (on day 2 and day 9, respectively), and each CSF was evaluated according to physical/cytochemical parameters. In the first sample, hypoglucorrachia (35 mg/dL) was observed, and in the second sample, hyperproteinorrachia (58 mg/dL). Each CSF was centrifuged at 2,500 revolutions per minute (rpm) and the sediment was cultured in Columbia agar with 5% lamb blood (Ref 211125 Becton Dickinson) and MacConkey agar II (Ref 254447 Becton Dickinson), and incubated at 37 °C. Each one was smeared for Gram stain and Indian ink mounting. Both CSF samples presented clear, colorless appearance, with pH 8.5 and pH 8.0, respectively; leukocytes were within normal and no red blood cells; Indian ink test from the second CSF sample was reported positive for capsulated blastoconidia. Isolation was possible only from the second CSF sample after culturing in Sabouraud Glucose agar and identifying creamy colored colonies 72 hours later with typical micromorphological features. The isolate was reported as *Cryptococcus* spp. Antifungal therapy was initiated with amphotericin B-AmB (27 mg IV daily) and fluconazole- FCZ (170 mg IV daily) after the laboratory report. However, the patient's general condition greatly deteriorated; he entered a coma and died after thirteen days of hospitalization.

Samples and isolates of *Cryptococcus* spp. were subsequently referred to the National Institute of Health for identification and serology of CSF was reported positive (1:2048) with cryptococcal antigen latex agglutination test (CALAS) (Meridian Bioscience, INC., OH, USA); microbiologically, the isolate was phenotypically positive for capsulated blastoconidia through Indian Ink test, as well as melanin production in *Guizotia abyssinica* media, urease production and *Cryptococcus gattii* was identified after the isolate grew in canavanine-glycine-bromothymol blue (CGB) agar turning the media to a blue color. Molecular typing was performed according to the protocol described by Meyer *et al.* (2003) and finally, the molecular pattern VGII was determined [5].

Discussion

As reported previously, cryptococcosis is a systemic mycosis with low prevalence in underage patients. Regarding Colombian minors, Lizarazo *et al.* reported that almost half (46.3%) of the patients in their study did not have underlying conditions. Other reports about this mycosis in underage patients in Brazil, Cuba, China and Taiwan indicate that in most cases there were no risk factors associated [3,6-8]. Almost 20% of patients diagnosed with cryptococcosis in many health care facilities are clinically non-immunocompromised and there is evidence that within this population, innate or acquired immunodeficiencies may underlie [6,9]. The case we report here is about a non-HIV patient without remarkable previous medical issues and it is important to note that no complementary immunological studies were done.

In terms of age and gender, Lizarazo *et al.* reviewed some reports from Thailand, China and Brazil regarding

children with cryptococcosis without any known risk factors. An average age of 9.7 years and predominance of the male sex was found which is consistent with this case and with the findings of the Colombian study. As for clinical manifestations such as headache, vomiting, confusion, fever, meningeal signs, visual disturbances, seizures, these are known to be neurological manifestations of cryptococcosis. Intense headache, vomiting and confusion were present in this case as well as in the Colombian children study where the most frequently reported symptoms were headache (78.1%), fever (68.8%), nausea and vomiting (65.6%), confusion (50%) and meningeal signs (37.5%). Except for the fever and meningeal signs not observed, clinical findings in this case are consistent with those found by other authors [3,6-8,10].

The determinants of mortality and outcome of patients are less well defined in *C. gattii* infections, but it has been described that masculine gender, altered state of consciousness and a history of seizures before starting treatment, are associated with higher mortality rates [10]. In addition, infection by *C. gattii* is associated with more severe neurological complications than by *C. neoformans* and permanent neurologic sequelae (blindness, deafness and others) may be more severe in this group, so careful examination and complementary immunological tests could clarify many questions and establish differences with respect to HIV-infected patients in terms of epidemiology, clinical course, diagnosis and outcome of this mycosis [6,10]. In this fatal case, the patient presented pulsatile headache, aphasia and altered mental condition before hospital admission, which continued throughout his hospital stay until death. In contrast to this outcome, Debourgogne *et al.* reported a case of cryptococcosis by *C. gattii*, VGIIb in a five-year-old girl without known risk factors who presented drowsiness and increasing respiratory pauses; after opportune diagnosis and treatment with amphotericin B deoxycholate (paediatric dose of 1 mg/kg QD) and 5-flucytosin (paediatric dose 0f 25 mg/kg QID), the patient overcame her condition [11].

Regarding laboratory findings, the diagnosis of cryptococcosis was possible from CSF, which is consistent with the predominant fungal neurotropism reported by other investigators [3,6]. The sensitivity of Indian ink test is low and visualization of typical capsulated blastoconidia was possible in the current case with the second sample of CSF. Moreover, although culture is the gold standard for detection of *Cryptococcus* spp., isolation was also difficult since the first attempt was unsuccessful and only possible with the second sample of CSF. In addition, antigen from CSF (made post-mortem) proved to be positive (1:2048) indicating a very high concentration which correlates with the fatal outcome of the patient.

Regarding the distribution of the four major molecular types of *C. gattii*, several reports confirm that molecular type VGII is highly prevalent in both North and South America. Some studies even propose that its origin is from South América [10]. Furthermore, accurate identification of *C. gattii* can be more difficult in non-endemic regions because routine microbiologic methodologies in health facilities do not differentiate between species. In this case, determination of *C. gattii* as well as identification of molecular pattern VGII was achieved post mortem after the sample and isolate were forwarded to the National Reference Center.

Although case reports of *C. gattii* infections are scarce in America, data from Northern and Northeastern regions of Brazil indicate high prevalence rates in children (47% from the state of Pará; 9.5% from the state of Piauí), especially cases from rural settings [2,12,13]. In another study from the state of Bahia, the authors did not establish differences among complexes species of *Cryptococcus* isolated but reported that 1/3 of the population with cryptococcosis were children under 15 years of age [14]. As previously presented, in Colombia the prevalence of cryptococcosis (1993-2010) in minors is low (2.6%) but a study from the northeastern region of the country that compared clinical findings between HIV+ and non-HIV patients, indicated an unexpectedly higher prevalence (29.6%) in children under 16 years old which is coherent with previous results in Brazil [2,12-15]. These significant findings provide valuable insights for better understanding the epidemiology of cryptococcosis in Latin America. The patient described in our case report belonged to an indigenous community located in the tropical desertic territories between Colombia and Venezuela where most of the population lacks formal education; their economy is based on herding goats and sheep, starting from early age. Considering that cryptococcosis by *C. gattii* occurs also in goats, we cannot rule out the possibility of associating this risk factor with the case; however, this was not inquired while the patient was hospitalized.

High mortality rates due to meningeal cryptococcosis occur especially in cases with late diagnosis, and because it is the most common fungal infection of the central nervous system, it is important to consider cryptococcosis within differential meningeal pathologies, especially in pediatric patients

who reside in rural environments with limited opportunities to receive timely health care.

Ethical Responsibility

The authors declare to have written authorization of the Scientific Direction of the Institution where the patient was hospitalized to publish the present case which is faithfully adjusted to the information recorded in the clinical history following valid ethical standards to preserve the patient's identity.

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