



Case Report/Relato de Caso

Cryptococcus gattii meningoencephalitis in an HIV-negative patient from the Peruvian Andes

Meningoencefalite causada por *Cryptococcus gattii* em um paciente HIV-negativo procedente dos Andes Peruanos

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ABSTRACT

We report a case of an immunocompetent Peruvian patient from the Andes with a one-month history of meningoencephalitis. *Cryptococcus gattii* was identified from a cerebrospinal fluid culture through assimilation of D-proline and D-tryptophan as the single nitrogen source. Initially, the patient received intravenous antifungal therapy with amphotericin B. The patient was discharged 29 days after hospitalization and continued with oral fluconazole treatment for ten weeks. During this period, the patient showed clinical improvement with slight right-side residual weakness. Through this case report, we confirm the existence of this microorganism as an infectious agent in Peru.

Key-words: *Cryptococcus gattii*. Meningoencephalitis.

RESUMO

Nós reportamos o caso de um paciente peruano imunocompetente proveniente dos Andes com história de um mês com meningoencefalite. Foi identificado o *Cryptococcus gattii* na cultura de líquido cefalorraquidiano através da assimilação de D-prolina e D-tryptofano como fonte única de nitrogênio. Inicialmente, o paciente recebeu tratamento antifúngico intravenoso com amfotericina B. O paciente foi liberado 29 dias depois da hospitalização, seguindo tratamento oral durante 10 semanas com fluconazol. Durante este período, o paciente apresentou melhora clínica e uma leve fraqueza residual direita. Com o reporte do caso, nós confirmamos a existência desse microorganismo como agente infeccioso em nosso país.

Palavras-chaves: *Cryptococcus gattii*. Meningoencefalite.

INTRODUCTION

Cryptococcus neoformans is subdivided in three varieties and five serotypes: *Cryptococcus grubii* (serotype A), *Cryptococcus neoformans* (serotypes D and AD) and *Cryptococcus gattii* (serotypes B and C)¹. *C. gattii* (serotypes B and C) is mainly found in tropical and subtropical climates, predominately affecting immunocompetent individuals, and is isolated from a variety of environmental

sources¹. Meningoencephalitis caused by *C. gattii* in apparently immunocompetent HIV-seronegative individuals occurs throughout tropical latitudes, and particularly in parts of South-East Asia and Australia¹.

In Peru, it is known that *C. gattii* produces infection in humans, and this has previously been reported in the literature². However, none of these patients were from high-altitude lands. We present a report on meningoencephalitis due to *C. gattii* in an HIV-negative patient who was from the Andes.

CASE REPORT

A 54-year-old male from Lircay, a rural area located at 3,372m above sea level (latitude 12° 58' 55.3", longitude 74° 43' 5.9"), near Huancavelica, Peru, started to complain of mild to moderate headache, hyporexia and irritability a month before admission. Additionally, he had a strength deficit in the lower limbs, which impaired his gait, along with hallucinations and sustained incoherent conversation. Ten years earlier, he made a trip to the Peruvian jungle (Satipo), where he worked for three months as a logger. He did not have any significant past medical history and he said that had not been using alcohol or medications. He was currently a farmer, growing potatoes and other tubers, and he used to raise hens and guinea pigs. In the physical examination, he was disoriented and was positive for right hemiparesis, Babinski's sign, nuchal rigidity, Brudzinski's sign and Kernig's sign, with normal funduscopy results. The score on the Glasgow scale was 14/15 (motor 6, verbal 4 and eyes 4).

Hematological and metabolic panels were normal, except for low lymphocyte levels: white cell count (WCC) of $9.5 \times 10^9/l$ (10% lymphocytes). The enzyme-linked immunosorbent assay (ELISA) for HIV and the TB series in sputum, feces and urine were all negative. A CT scan of the brain showed diffuse cerebral edema, asymmetrical cavities and a hyperdense nodular lesion on the left side of the frontal area, which did not enhance with contrast (**Figures 1A and B**). Cerebrospinal fluid (CSF) examination showed a large number of cryptococci through India ink staining, with WCC of 240 cells/mm³ (lymphocytes: 90% polymorphs 10%), protein level of 164mg/dl, positive Pandy test, glucose of 12mg/dl and negative for adenosine deaminase (ADA). Gram and Ziehl-Nielsen stains on CSF were negative. Culturing on Sabouraud's agar showed *Cryptococcus*, and the presence of *C. neoformans* was confirmed through a positive urease test and auxanograms for sugars. The D-proline and D-tryptophan

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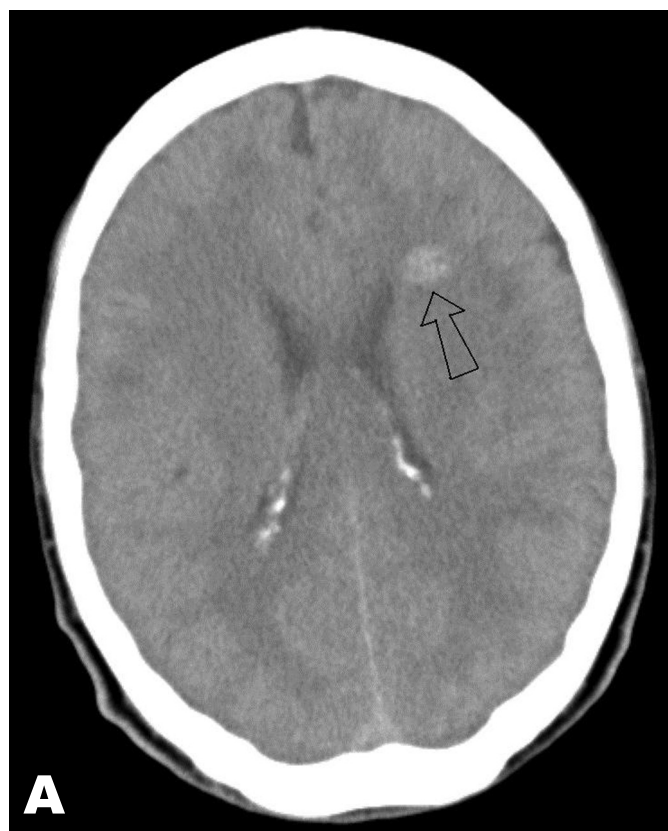


FIGURE 1A/1B - Diffuse cerebral edema with nodular lesion in the front left region, presumed to be a cryptococcoma.

assimilating test with incubation at 25°C and readings at 48 and 72h was considered positive because of abundant growth around the disc impregnated with D-proline (Himedia, Mumbai, India) and D-tryptophan (Difco, Detroit, MI, USA) on carbon-base agar. *C. gattii* was identified through its ability to use these D-amino acids as the single source of nitrogen. In the worldwide literature, it has been shown that D-proline and growth on L-canavanine glycine bromothymol blue medium have similar efficiency in relation to isolation of *C. Gatti*³.

Treatment with intravenous amphotericin-B at 0.7mg/kg was started. After three days of administration of the drug, the patient developed hypokalemia episodes, consisting of around 2mmol/l. Administration of hyperkalemic fluids and diet were started.

The potassium levels became normal after seven days of use of the drug. Later, after 11 days of treatment, a cumulative dose of 535 mg of amphotericin-B was reached and the patient was switched to oral fluconazole 450mg daily, because of side effects.

A control lumbar puncture was performed on the 19th day of treatment, and India ink staining on this was positive for *C. neoformans*, but culturing was negative. The WCC was 80cells/mm³ (monocytes: 90%, polymorphs 10%); the protein level was 52mg/dl; the Pandy test was negative; the glucose level was 38mg/dl and the ADA test was negative.

The patient was discharged 29 days after hospitalization, and continued with oral fluconazole treatment (450mg/day) for ten weeks. During this period, the patient showed clinical improvement with slight right-side residual weakness. Later, the dose of oral fluconazole was decreased to 150mg/day and the patient returned to his hometown.

DISCUSSION

C. gattii has a predilection for invasion of the central nervous system (CNS) and causes disease primarily in immunocompetent hosts¹. The entry route for *Cryptococcus* is primarily through inhalation of the infectious spores from the environment. The initial pulmonary infection is generally asymptomatic, although self-limited pneumonia resolving over several weeks to months in the absence of treatment may be seen¹. Spreading to the CNS occurs through hematogenous dissemination, and resistance to infection is primarily dependent on cell-mediated immunity⁴. Studies on mice indicate that *Cryptococcus neoformans* crosses the blood-brain barrier through transcellular migration across brain endothelial cells and then proliferates in the subarachnoid space, thereby resulting in leptomeningeal opacification with a gelatinous appearance⁴.

Patients may present with acute, subacute or chronic meningitis, or meningoencephalitis⁵. These signs and symptoms are usually present for several weeks and include headache, fever, cranial neuropathy, alteration of consciousness, lethargy, memory loss, signs of meningeal irritation, and coma⁶. *C. gattii* has a predilection for causing disease in the brain parenchyma rather than in the meninges, thus resulting in more evidence of cerebral cryptococcoma or hydrocephalus. Although these lesions are chiefly observed in the cerebral hemispheres, they have also been reported in the cerebellum and spinal cord⁷.

The Infectious Diseases Society of America has proposed that the treatment should consist of amphotericin B, 0.7mg/kg/d, plus flucytosine, 100mg/kg/d, for 2 weeks, then fluconazole, 400-800 mg/d, for at least 10 weeks. The combination of amphotericin and flucytosine is known to be the most rapid fungicidal regimen during the first two weeks of the treatment¹.

Our patient received amphotericin alone for 11 days. After that, he was switched to oral fluconazole for 10 weeks. We did not have the amphotericin/flucytosine combination available, but we observed that the clinical response was good and that the CSF culture was sterile after 19 days of treatment.

In Peru, there has only been one previous retrospective report on *C. gattii* isolation. This was on two immunocompetent patients² who came from areas with a warm climate and altitude lower than 2,400m above sea level, located on the coast and in the cloud forest.

The first patient had a tumor in his leg without any neurological condition, and did not show improvement with amphotericin B. The second patient presented chronic meningoencephalitis with neurological sequelae due to hydrocephalus following treatment with amphotericin B.

Our patient came from an area where the climate is temperate and dry, with a median temperature between 11°C and 17°C. This location is 3,372m above sea level. Native flora and fauna exist in this area, but are only found outside the rural villages. Thus, it would be difficult to conclude that the patient might have acquired the infection from certain native plants which might be reservoirs for *C. Gatti*. Reforestation using *Eucalyptus camaldulensis* and *E. tereticornis* was attempted in this area, but it was unsuccessful because of the Andean climate. These two *Eucalyptus* species appear to be the main reservoir for the organism. However, as described above, the acquired infection was diagnosed in an area without eucalyptus trees, thus indicating that other environmental sources might exist. Currently, 32 tree species belonging to diverse genera and families have been reported to harbor one or more *Cryptococcus* varieties⁸.

In Canada, research studies have demonstrated that *C. gattii* inhabits low altitude areas (less than 770m above sea level, and at an average altitude of around 100m), in locations where the average temperature is higher than the temperature in adjacent land⁹.

We did not find any other studies describing *C. Gatti* in high-altitude areas. There is the chance that the patient might have acquired the infection in the place where came from originally. Another possibility is that the patient might have acquired *Cryptococcus* infection while he was working in the Peruvian jungle. The infection was probably latent in his pulmonary system and then spread hematogenously to the CNS. Unfortunately, we did not run tests to rule out immunodeficient conditions such as cancer or idiopathic T CD4 lymphocytopenia¹⁰, which might be associated with this type of infection.

In conclusion, the existence of this microorganism as an infectious agent has been confirmed in our country. This is the first patient from the Andes. The possibility that the patient acquired the infection in another location when he worked as a logger in the jungle ten years earlier could not be ruled out, but this would be very unlikely. In Peru, the source of infection has not yet been determined, because of the extensive biodiversity and small numbers of studies. It is important to consider the likelihood that this infection may occur not only among patients coming from tropical and subtropical regions but also among patients coming from mountainous regions.

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