Neuromeningeal cryptococcosis in HIV-uninfected patient: a case report

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Abstract

We report a 24-year-old female patient with a neurological deficit without fever or meningeal syndrome. HIV serology was negative and CD4 count was normal. Cerebrospinal fluid analysis revealed the presence of Cryptococcus neoformans. Neuromeningeal cryptococcosis was suspected. The initial course was favourable with antifungal therapy.

Neuromeningeal cryptococcosis in HIV-uninfected patient: a case report

Short title: Cryptococcosis in immunocompetent patient

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ABSTRACT

We report a 24-year-old female patient with a neurological deficit without fever or meningeal syndrome. HIV serology was negative and CD4 count was normal. Cerebrospinal fluid analysis revealed the presence of*Cryptococcus neoformans* . Neuromeningeal cryptococcosis was suspected. The initial course was favourable with antifungal therapy.

KEWORDS

case report, cryptococcal meningitis, Cryptococcus neoformans, HIV-negative

KEY CLINICAL MESSAGE

Cryptococcosis is common in HIV-uninfected patients. Testing for *Cryptococcus* should not be limited to immunocompromised patients. The Indian ink staining technique should be used routinely for any cerebrospinal fluid analysis.

INTRODUCTION

Cryptococcosis is a mycotic disease that usually occurs in immunocompromised patients, particularly those infected with the Human Immunodeficiency Virus (HIV) [1]. The most common clinical form is meningoencephalitis, which is fatal if untreated. In the literature, cases have been reported in immunocompetent patients, remaining unusual forms [2]. We report a new case of neuromeningeal cryptococcosis in an HIV-uninfected patient.

OBSERVATION

A 24-year-old woman was admitted to the Department of Internal Medicine with functional impotence of the right hemisphere. The disease had started 6 days before admission with a sudden onset of abnormal movement of the right upper limb followed by functional impotence of the right hemisphere, headache and aphasia. The general condition was altered without fever.

In the history, she was 5 months postpartum, not immunocompromised, and did not have long-term corticosteroid therapy or recurrent infection. She was neither diabetic nor hypertensive.

Physical examination revealed right hemiparesis and Broca's aphasia. She was conscious and had no intracranial hypertension or meningeal syndrome. She had bilateral, painless oedema of the lower limbs, hepatalgia and hepatojugular reflux.

The blood count was normal with no lymphopenia (lymphocytes 1709/mm3) and the C-reactive protein was negative. Serum creatinine, ionogram and liver function tests were normal. HIV and hepatitis serologies were negative. The polymerase chain reaction test for SARS-COV-2 was negative.

Serum protein electrophoresis revealed hypoalbuminemia (29.48 g/L) with no abnormalities in other fractions (alpha-1 2.97 g/L, alpha-2 6.88 g/L, beta-1 4.35 g/L, beta-2 2.20 g/L, gamma 9.13 g/L). The CD4 T-cell count was $508/mm^3$.

The brain CT scan showed left parietal hypodensity with meningeal enhancement and cortico-frontal calcification raising suspicion of meningoencephalitis (**Figure 1**).

Cerebrospinal fluid (CSF) examination revealed clear fluid with high pressure, normal cellularity, normal glucose (2.63 mmol/L) and protein (0.25 g/L) levels and sterility on routine direct examination. *Cryptococcus neoformans* was present on Indian ink staining.

Due to the asthenic context and the SARS-COV-2 epidemic, a chest CT scan was performed and showed images consistent with infectious lung disease.

Transthoracic echocardiography showed left chamber dilatation, high left ventricular filling pressure, global hypokinesia suggestive of heart failure with impaired ejection fraction (38%).

The diagnosis of neuromeningeal cryptococcosis in non-immunocompromised patient was retained. The presentation was associated with decompensation of postpartum heart disease and bacterial pneumonia.

Amphotericin B injection 1 mg/kg was started for 2 weeks, followed by Fluconazole cp 400 mg daily for 6 weeks. Lumbar CSF drainage was performed. Pneumopathy was treated with CEFTRIAXONE IV 1g for 7 days. The rest of the management consisted of treatment of cardiac disease and clinical-biological monitoring.

After 3 evacuation sessions, the CSF pressure had normalized. The neurological evolution was favourable with regression of the hemiparesis and aphasia on the 7th day. Hemodynamic parameters were stable and

signs of cardiac decompensation had disappeared.

Three months after hospitalisation, the patient had died at home. The cause of death has not been determined.

DISCUSSION

Cryptococcosis is one of the most common invasive fungal infections with a variable prevalence. In the United States, the annual incidence is 0.8 cases per 100,000 population [3]. In France, the prevalence is 0.2 cases per 100,000 population [4]. In African regions, which are most affected by HIV, it is the main cause of infectious meningitis [5].

The causative agent is an encapsulated yeast that is usually transmitted by inhalation of fungal spores. *Cryptococcus neoformans* is found in soil, wood and bird droppings. *Cryptococcus gattii* is mainly found in tropical regions [6].

Cryptococcosis is the second most common opportunistic infection in AIDS after toxoplasmosis. According to the World Health Organisation classification, it is included in stage 4 of HIV infection, affecting patients with a CD4 count of less than $100/mm^3$[7].

Cases have been reported in HIV-uninfected patients with haematological malignancy, cancer, diabetes, cirrhosis, systemic disease and immunosuppressive therapy [8,9,10,11]. Cryptococcosis in non-HIV patients is often associated with an underlying disease and remains an unusual form. Men are most commonly affected according to observations [9,12,13,14]. In our case, the patient presented with concomitant heart failure.

Cryptococcosis is one of the infections with a neurotropism. Cryptococcal meningitis has a highly variable prevalence, ranging from 2.1% to 35.8% in sub-Saharan Africa [15]. Clinical manifestations are often less typical of meningitis, making diagnosis difficult [11]. Headache and fever are frequently reported. Convulsion, confusion and neurological deficit are rarely described. Diagnosis is based on direct examination for *Cryptococcus* using India ink staining, cryptococcal antigen testing or culture on Sabouraud medium. Biochemical analysis of CSF may show neither hypercytosis nor hyperproteinorachy.

The neurological picture presented by our patient directed us in first intention towards a vascular or tumoral etiology, reinforced by the absence of fever and meningeal syndrome. The lumbar puncture was performed only after the result of the brain CT scan. The clinical polymorphism of neuromeningeal cryptococcosis may delay diagnostic and therapeutic management. The Indian ink staining technique should be performed routinely for all CSF analysis, regardless of the patient.

For immunocompetent hosts with the neuromeningeal form, the standard treatment is a combination of Amphotericin B and Flucytosine for 6-10 weeks. An alternative is a 2-week treatement followed by Flucanazole for a minimum of 10 weeks. Consolidation treatment with Fluconazole can be continued for up to 6-12 months, depending on the patient's clinical condition [6]. Regular lumbar CSF drainage is recommended if the pressure is excessive. In this case, the patient received Amphotericin for 2 weeks and Fluconazole for 6 weeks.

Neuromeningeal cryptococcosis is a serious infection, progressing to death in the absence of treatment. The prognosis remains guarded even in immunocompetent patients. The mortality rate in HIV-uninfected subjects remains at around 15% in spite of well-conducted treatment. The rapid evolution of the symptoms, the presence of intracranial hypertension and disturbance of consciousness, the low cellularity in the CSF and hypoglycorrachia are factors of poor prognosis.

CONCLUSION

Cryptococcosis is common in HIV-uninfected patients. These patients often have a concomitant underlying disease. The neuromeningeal form is often atypical, delaying diagnosis. The search for *Cryptococcus*should not be limited to immunocompromised patients.

ABBREVIATIONS

CSF: Cerebrospinal fluid

HIV: Human Immunodeficiency Virus

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

AM Andrianiaina: followed up the patient, collected the clinical data and drafted the report. RMF Randrianarisoa, LN Rakotonirina SJN Ratsimbazafy: designed and critically revised the report.

HMD Vololontiana: validated the report.

All authors have read and accepted the final version of the article.

CONSENT TO PUBLICATION

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy

The patient has given informed consent for this publication. Only information necessary for scientific understanding was shared. Anonymity was respected.

DATA AVAILABILITY STATEMENT

All data generated are included in the article.

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FIGURE LEGENDS

FIGURE 1 Brain CT scan without and with injection

Left parietal hypodensity (A), meningeal enhancement (B) and parasagittal cortico-frontal calcification (C) suggestive of meningoencephalitis.