Neuromeningeal Cryptococcosis in a non-Immunocompromised Patient: Two Cases

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Neuromeningeal cryptococcosis (NC) , is a mycosis caused by an encapsulated yeast fungus, named *Cryptococcus neoformans* (CN) , primarily affecting immunocompromised patients, particularly those with human immunodeficiency virus (HIV), but may rarely affect immunocompetents. We report the observations of two immunocompetent adult patients with neuromeningeal cryptococcosis, they are fifty six years old and forty six years old, the disease started in both patients with symptoms of meningoencephalitis, the diagnosis was established by the presence of *cryptococcus* in the cerebrospinal fluid (CSF) and in the serum by the detection of the capsular polysaccharide antigen by latex agglutination. The search for the common etiologies causing the immunosuppressant has been negative. Amphotericin B treatment was started. The evolution was favorable in the first case and fatal in the second one causing his death with cerebral engagement. We conclude from these observations, that neuromeningeal cryptococcosis can occur in any patient immunocompetent.

INTRODUCTION

Obstructive jaundice is a common Cryptococcosis, is an opportunistic mycosis caused by yeasts of the genus *Cryptococcus*. The neuromeningeal localization of the infection is serious because of its high morbidity and mortality.

Cryptococcal infection is often diagnosed in immunocompromised patients, it is considered the most frequent systemic mycosis during HIV infection, but cases of cryptococcal meningitis have been reported in immunocompetent patients, and the number of cases has been increasing in the last few years **[1]**. Nevertheless, neuromeningeal cryptococcosis remains a rare entity in patients without underlying immune dysfunction. We present two cases of cryptococcal meningitis in two previously healthy men, the lumbar puncture showed cryptococcal infection. Without any conditions leading to immune compromise.

Observation 1:

Mr M.M, 56 years old, with no notable past history, notably no obvious cause of immunodepression, admitted to the neurology department for a febrile meningoencephalitis complicated initially by neurological disorders.

The neurological examination found a confused patient, with a Glasgow score of 14, who presented episodes of temporo-spatial disorientation at times, without deficits; with equal and reactive pupils.

An initial lumbar puncture (LP) was performed showing pneumococcal bacterial meningitis (WBC=200 RBC=1000 Neutrophils=60% lymphocytes =40% glucose =0.95 protein=1.62).

The patient was treated with a 3rd generation cephalosporin at a meningeal dose (Ceftriaxone : intravenous dose of 100 mg/ kg/day)

for 15 days. In view of the lack of clinical improvement (persistence of fever, meningeal stiffness and headaches), and the appearance of vertigo, a second LP and a cerebral CT scan were performed, and a cryptococcal search in the CSF and serum were requested.

Serum and cerebrospinal fluid capsular polysaccharide antigen testing by latex agglutination was performed, with a positive qualitative test and a quantitative CSF test titrated at 1/100 (Figures 1 and 2). The brain scan noted the presence of deep lacunar lesions.

Serologies: HIV, Hepatitis B and C, and Syphilitic were negative.

Treatment with amphotericin B (1 mg/Kg/day) in the induction phase for 2 weeks was started, followed by consolidation treatment with fluconazole (400 mg/day) for 2 months. An antigen test was performed one month later and revealed a regression of the antigen level to a titer of 1/10.

Observation 2 :

Mr Y.B, 46 years old, with no particular past history, except a chronic alcoholism weaned 2 years ago, having presented one week before his hospitalization in the neurology department with a syndrome of intracranial hypertension (IHT) with notion of hallucination and fluctuating confusion without associated convulsive seizures

The clinical examination on admission showed a conscious patient who was hemodynamically and respiratorily stable. Very cephalalgic, with a cerebellar syndrome on neurological examination, without other associated signs

The patient underwent an LP showing bacterial meningitis with a predominance of PNN, and was initially treated with a 3rd generation cephalosporin at a meningeal dose. The evolution was marked by the appearance of febrile peaks with episodes of agitation. A second LP with a cerebral MRI was requested.

The mycological examination of the CSF found on direct examination with Indian ink the presence of encapsulated round yeasts with a peripheral halo, characteristic of *Cryptococcus neoformans* (Fig. 3). The detection of circulating cryptococcal antigens by latex agglutination in the CSF and serum was positive at a titre of 1/4096.

The brain MRI showed some T2 flair punctiform hypersignals involving the supratentorial white matter of non-specific vascular appearance. The workup for underlying immunodepression, including HIV serology, was negative.

An attack treatment with amphotericin B (1 mg/Kg/day) was started. A few days later, the patient presented respiratory distress and progressively worsening consciousness, which led to his stay in an intensive care unit for several days. His neurological condition continued to deteriorate, leading to death in a cerebral engagement.

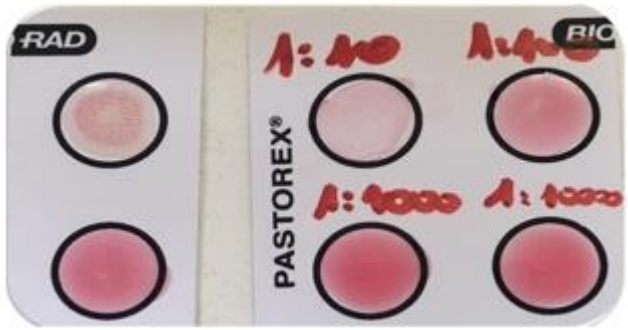

Figure 1: Positive qualitative test and positive quantitative test titrated at 1/100.

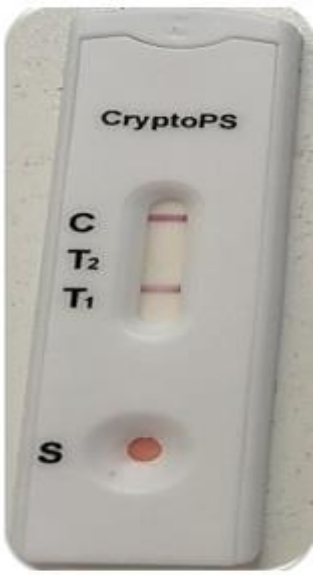

Figure 2: Rapid serum test positive for *Cryptococcus neoformans*.

Figure 3: Direct examination of the CSF showing the presence of an encapsulated round yeast identifiable by Indian ink (Magnification power X 40).

DISCUSSION

Neuro-meningeal cryptococcosis is a serious affection, which is due to a opportunistic yeast that occurs in immunocompromised people especially HIV+ patients with CD4 count lower than 200 CD4/mm^3 **[2,3]**. In immunocompetent hosts, neuromeningeal cryptococcosis, without clearly identified risk factors, is a difficult diagnosis and is often misdiagnosed as a viral or bacterial infection.

Although malignancy, drugs, genetic deficiencies, and AIDS are well known causes of immunosuppression, it is important to consider that several conditions, including alcoholism, diabetes mellitus, cirrhosis, and autoimmune conditions can be considered mildly immunosuppressive states, which may predispose hosts to opportunistic infections **[4]**. Howaver, for our 2 patients, they were considered as immunocompetent subjects because they did not have in their history situations that induce an immunodepression, notably a hemopathy, a neoplasia or an autoimmune disease. Also, they had no notion of long-term treatment with corticosteroids or immunosuppressants and the check-up carried out did not objectify diabetes or hepatic or renal insufficiency and also the serologies of hepatitis B and C as well as the HIV serology were negative. Neverthless, for the second clinical case mentioned above, although the exact predisposing factor could not be fully determined, it can be estimated that the cryptococcal infection could be related to his previous alcohol abuse. Although the patient abstained from drinking for 2 years before the onset of symptoms.

The central nervous system is the preferential site of cryptococcosis, which presents as meningoencephalitis in 69% of HIV-negative subjects and 90% of HIV-positive subjects **[5]**, **[6]**. Nevertheless, the neuromeningeal localization of cryptococcosis in immunocompetent individuals is not exclusive, it can reach different organs during disseminated infection, Indeed, studied cases have reported that other localizations can be associated; notably cutaneous **[7, 8,9]**, pulmonary endo-bronchial **[7, 9,10]**, urinary **[7]** and bone **[9]**.

The positive diagnosis of neuromeningeal cryptococcosis is based on mycological analysis of CSF, where direct examination with Indian ink detects encapsulated round yeasts of the genus *Cryptococcus* **[5]**, and on the culture on sabouraud chloramphenicol medium without actidione, which is positive in 48 to 72 hours. However, the detection of cryptococcal capsular antigen in various biological fluids by latex agglutination test remains the reference method for confirmatory diagnosis, it is a simple, rapid and reliable technique with a sensitivity of 95%. Antigen titration has a high prognostic value and a titer > 1/512 is associated with a high mortality, which explains the rapidly unfavorable evolution of our second patient whose antigen titer was 1/10 000.

Amphotericin B is usually combined with intravenous 5-fluorocytosine remains the treatment of choice for neuromeningeal cryptococcosis. In case of intolerance to one of the molecules, high-dose fluconazole (800 mg/d) combined with 5-fluorocytosine can be used as an alternative treatment **[11]**. In all cases, without treatment, the evolution of the disease will lead inevitably to death.

In Morocco, observations of neuromeningeal cryptococcosis in patients without risk factors of immunosuppression are few. In fact, a 21-year study of 40 cases of neuromeningeal cryptococcosis at the ibn sina hospital in Rabat revealed 2 cases of neuromeningeal cryptococcosis in which no immunosuppressive factors were found **[7]**, In addition, other cases have been described, notably in Morocco **[12]**, in America **[3]** and in Senegal **[13]**, confirming the presence of sporadic cases of cryptococcosis without any immunosuppression factor, in particular HIV.

CONCLUSION

Neuromeningeal cryptococcosis is a rare entity in immunocompetent subjects; it is not routinely sought in the presence of a neuromeningeal syndrome. These observations remind clinicians that any neuromeningeal syndrome in the absence of any immunosuppressive background should be considered as a fungal meningoencephalitis, such as neuromeningeal cryptococcosis.

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Ethical consideration: All the information gathered from the patients was handled confidentially, and it was used only for research purpose.

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HIGHLIGHTS:

- Cryptococcosis is a serious opportunistic mycosis caused by a fungus of the genus Cryptococcus neoformans.
- It occurs most often in patients with a significant deficit of cellular immunity and preferentially affects the central nervous system.
- It is less often suspected in immunocompetent patients, which leads to a delay in diagnosis and treatment.
- Its early diagnosis is necessary and its exploration

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