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CASE REPORT

Fungal Meningitis in an Immunocompetent Patient

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Abstract Cryptococcal meningitis is a rare entity among immunocompetent hosts but, when it occurs, it is associated with significant morbidity and mortality. Clinical presentation as well as the course of the disease is usually subtle and indolent with headache and altered mental status. The authors present the case of a 59-year-old man, who sought medical help with a 2-week history of headaches accompanied by nausea and visual and hearing disturbances. On admission the patient was afebrile, presented visual and hearing deficits and had a normal magnetic resonance image of the brain. A lumbar puncture was performed and microscopic examination of the cerebrospinal fluid revealed yeasts that were identified as *Cryptococcus* spp. and later, by means of molecular biology techniques, as *Cryptococcus neoformans*, var. *grubii.* The patient was treated with liposomal amphotericin B plus fluconazole for 28 weeks. At follow-up after 1 year the patient was asymptomatic and received fluconazole 400 mg/day as prophylactic therapy. The outcome of *Cryptococcus* infections in immunocompetent hosts is reported to be poor as a result of a delayed diagnosis and suboptimal initial antifungal therapy. The influence of the normal immune response is unclear.

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1 Introduction

Cryptococcus spp. are important fungal pathogens worldwide. Cryptococcal meningitis is the fourth most common life-threatening opportunistic infection in individuals with AIDS [1], but is rare among immunocompetent hosts [2, 5]. Cryptococcosis is a systemic mycosis associated with significant morbidity and mortality [3]. Its course is invariably fatal when left untreated [4]. Clinical presentation as well as the course of the disease is usually subtle and indolent with headache and altered mental status. The impact of the normal immune response is unclear [4]. The most common symptoms are headache and altered mental status, including personality changes, confusion, lethargy, obtundation, and coma [4]. Clinical suspicion is crucial because meningeal signs may be lacking. A lumbar puncture with microbiological examination of the cerebrospinal fluid (CSF) is diagnostic. *Cryptococcus neoformans* is the prevalent causative agent in cryptococcal infections among immunocompromised patients.

2 Case Report

A 59-year-old Brazilian man, living in Portugal for 8 years and working as a construction painter, visited our hospital

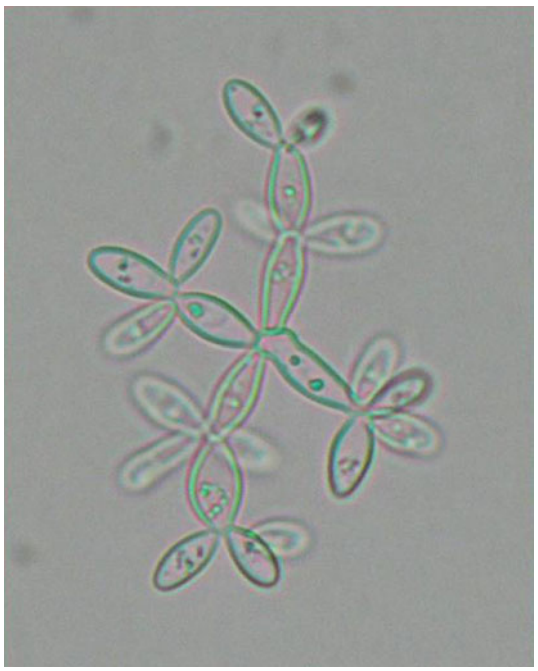

Fig. 1 Analysis of CSF at initial lumbar puncture showing *C. neoformans*, var. *grubii* (week 1)

Fig. 2 Analysis of CSF at initial lumbar puncture showing *C. neoformans*, var. *grubii* with a specific reagent for an improved identification of the causative agent (week 1)

with complaints of a progressive pulsating frontal headache accompanied by nausea and visual and hearing disturbances that had started 2 weeks earlier. Analgesics and anti-inflammatory drugs brought no relief. He denied having experienced fever, dyspnea, dysuria, diarrhea or any other symptom. He had a history of hypertension for which he never used medication.

On physical examination he had a blood pressure of 140/80 mm Hg and a regular pulse rate of 64 beats/min. His body temperature was normal. His mucous membranes were normal in colour, he was well hydrated and physical examination of the heart and lungs was unremarkable. The Glasgow coma score was 15, he presented with moderate hypoacusia and his visual acuity was diminished bilaterally, with limited abduction of the left eye and a binocular horizontal diplopia. There was no neck rigidity or any other meningeal sign.

Initial hematologic and biochemical analysis were normal: hemoglobin 13.7 g/L, leukocytes 5×10^3/UL with 900 lymphocytes, platelets $188 \times 10^3/\mu L$, normal renal and liver function tests, glucose 105 mg/dL and a C-reactive protein level of 1.1 mg/L. A computed tomography scan of the brain, with contrast, displayed no abnormalities. A lumbar puncture was performed; the opening pressure was greater than 50 mm H_20 and examination of the CSF revealed glucose 53 mg/dl, proteins 0.39 g/L and 13 cells.

Direct microscopic examination of the CSF, with India ink preparation, showed yeasts that were identified as *Cryptococcus* spp. (Figs. 1, 2). These yeasts grew very slowly in culture and were subsequently classified as *C. neoformans*, var. *grubii* by means of molecular biology techniques, namely analysis of the D_2 region of the fungal genome.

To map the neurological deficits the patient underwent a visual evoked potentials test, which showed that latency of waves P100, determined after individual stimulus of both eyes, was bilaterally substantially delayed. This finding was indicative of a severe neuroaxonal dysfunction of the optic pathway. The auditory evoked potentials test showed that the auditory pathways had also been affected bilaterally. Upper and lower limb evoked potentials proved normal. Hearing tests showed a plain bilateral neurosensorial hypoacusia. Visual campimetry disclosed an annular constriction, with an increase in the right eye blind spot in conjunction with a nasal constriction and increase in the left eye blind spot. Blood cultures were negative as were the serological assays for HIV, hepatitis B, hepatitis C and syphilis. CD4 cell count was 50.1 % and CD8 cell count was 15.8 %. Serum protein electrophoresis and immunoelectrophoresis were normal. Autoantibodies and other markers of systemic diseases were not encountered. Further examinations that included a computed tomography scan of the paranasal sinuses, a magnetic resonance imaging scan of the brain and the lumbar-sacral region, as well as a cerebral angio-magnetic resonance imaging did not show any abnormality.

The initial treatment consisted of liposomal amphotericin B at a dose of 3 mg/kg per day, but symptoms

persisted. As there was no clinical improvement, the dose of liposomal amphotericin B was increased to 6 mg/kg per day at week 4. At week 6, there was still no clinical or microbiological improvement and therefore fluconazole 800 mg/day was added, after which symptoms slowly improved. For symptomatic relief weekly therapeutic lumbar punctures were needed. The opening pressure remained increased and direct microbiological examination of the CSF with India ink preparation continued to reveal cryptococci, although they did not grow in culture. A total of 26 lumbar punctures was performed.

After 24 weeks of antifungal treatment, microscopic examination of the CSF showed no yeasts for the first time, but the patient continued to complain of moderately reduced visual acuity and severe hypoacusia. Liposomal amphotericin B was stopped at week 28 and he was finally discharged at week 32 under maintenance therapy with fluconazole 800 mg/day. While still in hospital he developed mild renal failure interpreted as secondary to liposomal amphotericin B, which improved after stopping the drug.

After discharge it was necessary to perform five more lumbar punctures. In the first two CSF samples occasional yeasts were still found but the last three were negative, although the opening pressure remained above the normal level. In January 2011, the date of the last lumbar puncture, he was asymptomatic under prophylactic therapy with fluconazole 400 mg/day. He continues to be under close surveillance and is seen at regular intervals at the Neurology Day Care Unit.

3 Discussion and Conclusion

This case highlights the importance of paying attention to clinical symptoms, even in the presence of initially negative laboratory and radiological investigations. The outcome of cases of *Cryptococcus* infection in immunocompetent hosts reported in the literature are poor as a result of three factors: a delayed diagnosis, suboptimal initial antifungal therapy and the normal immune response (a massive inflammatory process can cause havoc in a confined space such as the skull, which may contribute to intracerebral hypertension and increased disease severity) [3].

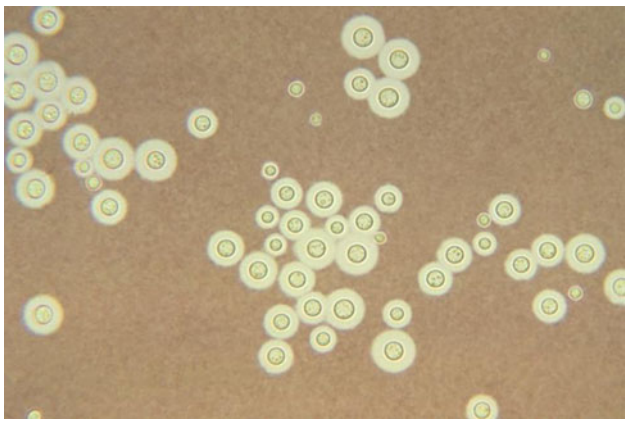

Fig. 3 The traditional aspect of *C. neoformans* using a light India ink staining preparation. This image is used to compare with Figs. 1 and 2 to illustrate the differences in shape (http://phil.cdc.gov/phil/details.asp?pid=3771)

In this particular case, there was no detectable immunodeficiency and the etiological agent was initially difficult to classify. The characteristic image of *C. neoformans* (Fig. 3) (http://phil.cdc.gov/phil/details.asp?pid=3771) is quite different from the CSF image seen in our laboratory (Figs. 1, 2). It was therefore necessary to apply innovative supplemental diagnostic methods, in particular molecular biology techniques to classify the fungus.

The use of higher doses of liposomal amphotericin B and the combination with another antifungal agent were, in spite of later reported in-vitro intermediate resistance to fluconazole, essential to achieve success. Moreover, it appeared necessary to prolong therapy with liposomal amphotericin B. Probably because of the prolonged therapy with high-dose amphotericin B, the patient developed renal failure that normalized after the suspension of the drug.

Early institution of therapy improves the prognosis of cryptococcosis. Amphotericin B in combination with flucytosine is the treatment of choice [3]. However, the latter drug is only available in Portugal on the basis of a case-by-case import, which makes it difficult to obtain in a timely manner. For this reason, this drug was not used as first-line therapy. The choice of liposomal amphotericin B was made because classic amphotericin B is no longer available in Portugal. Amphotericin B (classic and liposomal) have a poor penetration in the central nervous system, so an increase in the drug dose is frequently needed. On the other hand, fluconazole and flucytosine readily penetrate the central nervous system [6].

Cryptococcus meningitis is uncommon in immunocompetent hosts but it causes high mortality and long-term morbidity and should be considered in the differential diagnostic assessment of patients who complain of chronic headaches [2].

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