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Central Nervous System Cryptococcosis in Non-Immunosuppressed Patient

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Abstract

Cryptococcus is a fungus related to bird droppings (especially pigeons). It is described as an opportunistic pathogen. The leading defense against this fungus is the T-cell immunity, reason why it is related to immunocompromised patients (human immunodeficiency virus (HIV), organ transplant patients among others). The annual incidence is 0.4 - 1.3 per 100,000. The central nervous system (CNS) involvement is the most common manifestation in an immunocompromised patient; conversely it is a very uncommon manifestation in non-immunocompromised patients. A 32-year-old Hispanic male patient with no medical history, heterosexual and no toxics habits visited our institution, after visiting three emergency rooms for 1 week, complaining of general malaise, constant non-throbbing holocephalic headache 4/10 and low-grade fever of 12 days of evolution. Labs were unremarkable and vital signs showed fever of 38.6 °C. Physical exam was remarkable for neck stiffness. Patient was admitted with suspected meningitis. HIV test was negative and lumbar puncture showed increased opening pressure and India ink stain was positive. Patient was managed successfully with fluconazole. CNS cryptococcosis in non-immunosuppressed patients is extremely unusual. Diagnosis could be delayed because of low suspicious index in healthy population. Most experts recommend amphotericin B combined with flucytosine. Our patient was managed successfully with fluconazole IV followed with oral fluconazole. Patients from countries where flucytosine is unavailable and cannot tolerate amphotericin B can benefit from fluconazole.

Keywords: Cryptococcus; Meningitis; Immunocompetent

Introduction

Cryptococcus spp. are encapsulated yeast distributed worldwide. It tends to colonize the airway in non-immunosuppressed patients exposed to pigeon's excrement. Patients with immunocompromised status can develop disseminated cryptococcosis and/or central nervous system (CNS) involvement. The annual incidence is 0.4 - 1.3 per 100,000 in healthy population (no CNS), but it increases up to 2 - 7 cases per 100,000 in HIV patients [1]. CNS involvement is the most common manifestation in immunosuppressed patients [2]. Signs and symptoms are not different from other causes of meningitis [3]. In regard to meningitis due to *Cryptococcus*, the most common physical findings are: fever (100%), cephalea (100%) and neck stiffness (90%) [4]. Intact T-cell immunity tends to protect colonized population from CNS involvement, reason why cryptococcal meningitis is rare in non-HIV and non-transplant patients. For whether a patient presents with symptoms aforementioned, CSF must be analyzed. Characteristic findings of CSF include low glucose and high proteins. Elevated CSF opening pressure occurs in more than 50% of patients with cryptococcal CNS involvement [5]. Serial lumbar punctures (LPs) are required to decrease the opening pressure less than 200 mm H_2O. Neurosurgical evaluation for shunting is recommended for patients with persistent increased opening pressures despite of serial LPs [6]. Diagnosis of cryptococcal meningitis is determined if the patient met one of the following: CSF positive culture, positive India ink and positive cryptococcal antigen [7]. India ink staining sensitivity and specificity are 70.5% and 100%, respectively [8]. Current guidelines encourage the combination of amphotericin B plus flucytosine (B-II) [9], although studies have shown a successful rate of 72.7% with high dose of fluconazole.

Case Report

A 32-year-old Hispanic male patient with no medical history, heterosexual and no toxics habits, came to our institution, after visiting three emergency rooms for 1 week, complaining of general malaise, constant non-throbbing holocephalic headache 7/10 and low-grade fever of 12 days of evolution. Labs were unremarkable and vital signs showed fever of 38.6 °C. Physical exam was remarkable for neck stiffness. Head CT was performed and official was unremarkable. LP was performed collecting 13 mL of clear CSF, and sample was sent for cultures. Results were as follow: WBC 650, total protein 137, glucose 37, and mononuclear cells 100%. Opening pressure

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was elevated at 26 cm H_2O. Patient was admitted with diagnosis of meningitis. Vancomycin 1 g IV every 12 h combined with ceftriaxone 2 g IV daily was ordered. Later during same date, the physician was notified about India ink stain positive result. Crag test was not available to be ordered. Bacterial antigens for *H. influenza* type B, *Streptococcus pneumoniae*, *Streptococcus* group B, *N. meningitidis* A/Y, *N. meningitidis* B/*E. coli* K1, and *N. meningitidis* C/W 135 all returned negative. The physician ordered anidulafungin IV and consulted ID services. CSF culture did not recover any organism. However, ID services recommended discontinuing antibiotics and anidulafungin, and starting fluconazole 800 mg IV daily. HIV and immunoglobulins evaluation was recommended by ID service as well, returning unremarkable. LP was repeated after 7 days of treatment and showed an opening pressure of 19 cm H_2O with negative India ink stain. Patient was afebrile with no headache or neck stiffness. Fluconazole was continued at same dose completing 14 days, and then switched to fluconazole 400 mg PO daily for 10 weeks. Patient was followed every 2 weeks by ID service at outpatient clinics. Patient discontinued treatment at week 8 by himself. Symptoms aforementioned were not reported again.

Discussion

Cryptococcal CNS involvement mostly occurs in immunocompromised population with conditions such as AIDS. Organ transplant patients are at risk for developing cryptococcal CNS involvement as well. Our patient was immunocompetent with negative HIV test, unremarkable immunoglobulins and no history of cancer and developed cryptococcal meningitis. In tropical areas, mortality rate ranges from 0% to 38% in non-HIV patients [10]. There are some factors associated with increased mortality such as advanced age (over 60 years) and chronic organ failure [11]. Cryptococcal meningitis presents no pathognomonic symptoms that can differentiate from bacterial meningitis. More than 50% of patients have unremarkable head CT scan, as occurred with our patient [12]. Crag test was not ordered because it was unavailable. After LP, we recovered a positive India ink organism. Although CFS culture did not recover any organism, diagnosis of cryptococcal meningitis is determined if the patient met one of the following: CSF positive culture, positive India ink and positive cryptococcal antigen [7]. India ink staining sensitivity and specificity are 70.5% and 100%, respectively [8]. The novel antimycotic drugs, echinocandins, do not penetrate the brain blood barrier and should not be considered for treatment in cryptococcal meningitis [13]. Our case shows the successful treatment with fluconazole as monotherapy, an option to patients where the combination of amphotericin plus flucytosine cannot be offered. The patient was followed for 4 months, did not report headache and stayed afebrile with no neurological deficits.

Conclusion

CNS cryptococcosis is usually associated with an immunocompromised status and is a rare disease in immunocompetent patients that could be underdiagnosed. In view of low suspicious index, the diagnosis could be delayed. CNS cryptococcosis should be included as a differential diagnosis in all patients with suspected meningitis, regardless of the immune status. Patient must be evaluated with Crag (if available), India ink and CSF culture. Patients are diagnosed with CNS cryptococcosis whether they met one of the aforementioned criteria. Our case demonstrates that immunocompetent patients responded successfully to fluconazole as monotherapy. Further investigation should be conducted, in view to gather statistic information (incidence and mortality) of CNS cryptococcosis related to immunocompetent patients.

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Conflicts of Interest

We have no conflicts of interest to declare.

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