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Original Article

Cryptococcal Meningitis in Qatar: A Hospital Based Study From 2005-2015

Fahmi Yousef Khan[1], Mohamed Abu Khattab[2], Mohamed Abu Qamar[2], Muna Al Maslamani[2], Hussam Al Soub[2], Anand Deshmukh[3]

[1]Department of Medicine, [2]Department of Medicine, Infectious Disease Division, and [3]Department of Microbiology, Hamad General Hospital, Doha, Qatar

Abstract

Introduction: Cryptococcal meningitis (CM) is an opportunistic and life-threatening infection, affecting mainly patients with AIDS. The aim of this study was to estimate the prevalence of CM and describe its clinical profile, laboratory parameters, and outcomes in patients with CM in Qatar. **Patients and Methods:** This retrospective study was conducted at Hamad General Hospital. This study includes all patients admitted to the hospital with CM from January 1, 2005, to December 31, 2015. **Results:** Eleven patients were included in the study, representing 0.01% of the total admissions and 1.1% of all reported meningitis cases during the study; their mean age was 38.5 ± 12 years. Seven patients (63.6%) were males, and most of them were Filipinos. The most frequent presenting symptom was a headache. Six patients (54.5%) were HIV seropositive, three (27.3%) had preexisting immunosuppressive disorders, and two patients (18.2%) had no risk factors. All the patients tested positive in the cerebrospinal fluid (CSF) India ink examination and had a positive CSF culture for *Cryptococcus neoformans*. All patients received amphotericin B or liposomal amphotericin B with or without 5-flucytosine as induction treatment. Ten patients received fluconazole as consolidation/maintenance therapy. Eight patients (72.7%) were cured at the end of the treatment period. Two patients (18.2%) left before treatment completion, while one patient (9%) died during admission. **Conclusions:** CM is rare in Qatar and affects both HIV-positive and HIV-negative expatriates. Clinical presentation is nonspecific and requires a high index of suspicion.

Keywords: Acquired immunodeficiency syndrome, amphotericin B, cryptococcal, fluconazole, flucytosine, meningitis, voriconazole

Introduction

Cryptococcus neoformans is an opportunistic basidiomycete yeast that causes life-threatening infections, such as meningoencephalitis, mainly in patients with AIDS. However, patients with

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Address for correspondence: Dr. Fahmi Yousef Khan, Department of Medicine, Hamad General Hospital, Doha, Qatar.
E-mail: fakhanqal@aol.com

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other forms of immunosuppression as well as immunocompetent individuals may also be affected.[1-3] In humans, *C. neoformans* infection is acquired by inhalation of aerosolized particles containing yeasts or spores from the environment. In immunocompetent individuals, the resulting lung infection is often asymptomatic, and the initial lung infection site is normally healed or contained within granulomata that reflect a latent infection. The alteration in the host immune response can play an important role in the reactivation and subsequent hematogenous dissemination of the organism to the extrapulmonary sites, with a particular predilection for the brain that causes potentially life-threatening cryptococcal meningitis (CM).[3,4] This infection is responsible for an estimated 15% of all HIV-related deaths worldwide, three-quarters of them in sub-Saharan Africa. It is estimated that 223,100 cases of CM cause 181,000 deaths each year among people living with HIV.[5,6]

Although there is a marked increase in the incidence of CM around the world due to its association with AIDS, reports concerning this infection in the Arab countries, including Qatar, are limited.[2] The study aimed to estimate the prevalence of CM and describe its clinical profile, laboratory parameters, and outcomes in patients with CM in Qatar.

Patients and Methods

This retrospective study, conducted at Hamad General Hospital, involved all patients admitted to the hospital with CM from January 1, 2005, to December 31, 2015. The Hamad General Hospital is a 603-bed tertiary care center that covers all specialties except for hematology-oncology, cardiology, and obstetrics. It has been accredited by the Joint Commission International and Accreditation Council for Graduate Medical Education– International since 2016.

Case definitions

CM was diagnosed through the identification of *C. neoformans* from cerebrospinal fluid (CSF) by India ink staining, culture, or antigen testing. CSF and blood cultures were processed according to the standard methodology. For CSF samples, Gram stain, India ink preparation, and cryptococcal latex test (CALAS, Meridian Bioscience Inc., Newtown, Ohio, USA) were performed, followed by culture on Sabouraud dextrose agar. Plates were incubated at 37°C, and 25°C. Blood cultures received were incubated in Bactec system; once flagged positive, tests similar to CSF specimens were performed. All culture plates were read after 24 and 48 h. Identification was performed using API 20°C Aux (BioMérieux, Inc., Durham, North Carolina, USA) and rapid urease test. Minimal inhibitory concentration by means of E-test (BioMérieux, Inc., Durham, North Carolina, USA) was performed according to the CLSI standards (M27-A3 and M27-S4). The following antifungals were tested for susceptibility: amphotericin B, fluconazole, voriconazole, and flucytosine. As clinical cutoff values for cryptococcus are not still determined, the epidemiological cut-off values (ECV) were used as the reference.

Case identification and data collection

All cases were identified from the hospital's microbiology and infection control records. The files of the patients with CM were reviewed, and the following data were retrieved: Demographic information, clinical presentation, and underlying conditions; investigation results; information about isolates and antifungal susceptibility; treatment; disease complications and the outcome. The primary outcome was in-hospital mortality.

Data analysis

Data were analyzed using descriptive statistics, and continuous variables were expressed as means and standard deviations unless otherwise specified.

Results

During the study, 11 patients were identified, representing 0.01% of the total admissions and 1.1% of all reported meningitis cases during the same period. The mean age of the patients was 38.5 ± 12 years (Range: 26–64 years). Seven patients (63.6%) were male, and most of them were Filipinos [Table 1]. The most frequent presenting symptoms were headache, fever, and vomiting [Table 1].

Six patients (54.5%) were HIV seropositive, accounting for 5% of all HIV-infected persons

in Qatar during the study period. Among the HIV-infected patients, CM was the first presenting illness. None of them was aware of their HIV status prior to admission, and all were diagnosed only after admission. In addition, CM was the AIDS-defining infection in five patients (83.3%), as they presented with CD4+ T-cell count of <100 cells/μL. The rest of the cases were HIV-negative individuals. Among them, three patients (27.3%) had preexisting potentially immunosuppressive disorders, whereas two patients (18.2%) had no identifiable risk factors [Table 1].

All patients underwent lumbar puncture. CSF pressure was measured for 9 patients and was elevated in six patients (66.6%). All cases gave a positive CSF India ink examination and positive CSF culture for *C. neoformans*. The mean CSF glucose level was 2.8 ± 1.1 mmol/L (range: 0.6–4.8 mmol/L), while mean CSF protein level was 1.4 ± 1.5 g/dl (range: 0.2–5.5 g/dl). The CSF findings of the eleven CM episodes are listed in Table 2. Computed tomography scan data of the brain were available for all patients. Diffuse cerebral atrophy with ventricular dilatation was seen in one patient (9%).

Antifungal susceptibility results were interpretable for 9 of the 11 isolates [Table 3]. All patients were admitted to confirm the diagnosis and to receive treatment. In the induction period, which lasted for 2 weeks, four patients (36.4%) received amphotericin B, and seven patients (63.6%) received liposomal amphotericin B (AmB liposome) while five patients received flucytosine. One patient died after receiving one dose of amphotericin B. Following induction therapy, 10 patients received 400 mg of fluconazole as consolidation treatment for at least 8 weeks, followed by fluconazole 200 mg daily as maintenance therapy for 1 year. The mean duration of induction therapy was 12.9 ± 4 days (range: 1–14 days), the mean duration of consolidation therapy was 60.3 ± 4.7 days (range: 56–70 days), and mean duration of maintenance therapy was 299 ± 134 (range: 40–370 days).

Eight patients (72.7%) were cured at the end of the treatment period. Two patients (18.18%) left before treatment completion. One patient (9%) with HIV infection died during admission, and the rest of the HIV patients received antiretroviral therapy (ART) during the maintenance therapy.

Table 1: The demographic and clinical characteristics of the 11 patients involved

Variable	Value
Sex (%)	
Male	7 (63.6)
Female	4 (36.4)
Age (years), mean±SD (range)	38.5±12 (26-64)
Nationalities (%)	
Filipino	4 (36.37)
Indonesian	2 (18.18)
Somalian	1 (9.09)
Sudanese	1 (9.09)
Bangladeshi	1 (9.09)
Iranian	1 (9.09)
Indian	1 (9.09)
Clinical presentation (%)	
Headache	10 (90.9)
Fever	9 (81.8)
Nausea/vomiting	8 (72.7)
Altered mental status	4 (36.4)
Neck stiffness	3 (27.3)
Photophobia	2 (18.2)
Diplopia	2 (18.2)
Papilledema	2 (18.2)
Seizure	1 (9.1)
Underlying disease (%)	
HIV	6 (54.6)
Corticosteroid and immunosuppressive	3 (27.3)
Transplant receipt	2 (18.2)
Diabetes mellitus	2 (18.2)
Pneumocystis jiroveci	2 (18.2)
Ulcerative colitis	1 (9.1)
Pulmonary tuberculosis	1 (9.1)
Hypertension	1 (9.1)
Duration of symptoms (days), mean±SD (range)	16±7.7 (7-28)
Time from presentation to diagnosis (days), mean±SD (range)	5.7±1.3 (4-8)

SD: Standard deviation, HIV: Human immunodeficiency virus

Table 2: Cerebrospinal fluid analysis results in 11 patients with cryptococcal meningitis

Variable	Value
Opening pressure (cm H_2O)	122±82.6 (39-200)
Glucose (mmol/L)	2.8±1.06 (0.6-4.8)
Protein (g/dL)	1.4±1.5 (0.2-5.5)
WBC (/μL)	243.5±242.3 (50-777)
Lymphocytes	180.5±72.4 (60-200)
India ink (positive) (%)	11 (100)
Culture (positive) (%)	11 (100)
Antigen (positive) %)	10 (90.9)

WBC: White blood pressure

Table 3: Sensitivity to antifungal therapy

Antifungal agent	Sensitivity rate (%)
Amphotericin B	9/9 (100)
Fluconazole	9/9 (100)
Voriconazole	9/9 (100)
Flucytosine	9/9 (100)

Discussion

Despite the similarity of our results to other reports in the literature, the novelty of our work comes from the fact that we were the first to study CM in Qatar. It is recognized that within the genus Cryptococcus, two species cause life-threatening CM in humans: *C. neoformans* and *Cryptococcus gattii*.[3,6] As observed in our study, all isolates belonged to *C. neoformans*. This yeast has been classified into three serotype varieties: A (*C. neoformans grubii)*, D (*C. neoformans neoformans*), and AD (hybrids of serotypes A and D).[6] Serotyping is important since it allows for a better description of the epidemiological characteristics of these human pathogenic yeasts and could facilitate the timely application of adequate treatments and improve clinical surveillance strategies.[6] For example, serotype D, which is found predominantly in contaminated soil and bird droppings, has been implicated in the majority of CM cases in immunosuppressed patients, while serotype A is found in 74% of immunocompetent CM patients.[6-8] However, the clinical manifestations of human infections with serotype A or D appear to be similar, but experimental infections suggest that strains of serotype A are more virulent than strains of serotype D.[8] Due to the lack of facilities in our laboratory, the serotyping of our isolations has not been carried out. However, it seems that CM in our patients was caused by both serotypes because some of our patients were immunocompetent, and most of them were immunocompromised.

As noted in this study, and in agreement with a similar study,[9] all patients were expatriates from the most economically disadvantaged regions of the world and most probably acquired the disease many years earlier in their country of origin with reactivation of latent infection[3,4] on or after arrival in Qatar. The reactivation of latent infection is probably due to alteration in the host immune system that results from stress and poor socioeconomic conditions.

In agreement with other reports,[1,10-14] we found that the most consistent clinical features of CM were headache, fever, and vomiting. Other features included neck stiffness, photophobia, cough, and altered mental status. These presentations are not specific, making the definitive distinction between CM and other causes of meningitis, such as tuberculosis and brucellosis clinically unachievable.[15] Therefore, a high index of suspicion is required to avoid delays in reaching a definitive diagnosis. Hence, it is important to consider the possibility of CM during the investigation of all persons, including non-HIV patients, who present with chronic headache, especially in the presence of fever and neurologic deficits.[13,14]

Once CM is suspected, a lumbar puncture should be performed to confirm the diagnosis with India ink preparation or culture. The diagnostic yield of these modalities varies from one study to another. In recent studies, India ink staining was positive for CM in 82%–100% of the patients,[1,10,16-19] while CSF cryptococcal culture was positive in 90%–100% of the cases.[1,10,16,19] In our series, all patients had positive CSF India ink staining and cryptococcal culture; this falls within the stated range.

Once a diagnosis is established, antifungal therapy should be given in three phases (induction, consolidation, and maintenance).[20-23] Induction therapy with intravenous amphotericin B or liposomal amphotericin B (AmB liposome) with or without flucytosine is recommended for 2 weeks. After 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture), amphotericin B (or AmB liposome) and flucytosine can be discontinued, and consolidation therapy should be initiated with fluconazole at 400 mg daily for at least 8 weeks. Subsequently, the fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least 1 year of azole therapy.[20-24] In our series, all except one received the induction therapy, while

10 of them received the consolidation/maintenance therapy. The patient who did not receive the maintenance therapy died after 1 day of starting the induction therapy.

ART is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection.[25] However, none of our patients had received ART because HIV was discovered after infection have already developed. There is an overall consensus that ART should be initiated within the first 2 weeks in individuals with advanced HIV infection presenting with an AIDS-defining opportunistic infection, except for CM for which initial ART should be delayed at least 2–10 weeks after initiation of anti-cryptococcal therapy.[25,26] In our study, five patients with HIV infection received ART during maintenance therapy. Primary chemoprophylaxis with fluconazole is recommended for patients with CD4 cell counts <100 cells/μL.[27] However, a recent report[28] has shown that primary prophylaxis of cryptococcosis may not be beneficial, as survival rates and incidence of newly diagnosed cryptococcosis cases did not differ from those who did not receive fluconazole.

Globally, the mortality rates among treated patients were between 20% and 60%,[9] while in our study, it was 9%, which was below the global range. This rate could be explained by the fact that this study did not include a long-term follow-up on the patients to ascertain the true mortality rate. Moreover, two of our patients left the country before completing their treatment.

Some limitations of the study are noteworthy. First, it was retrospective, and thus there was no long-term follow-up to study relapses and determine the true mortality rate. We also obtained no information on drug toxicity. Second, cryptococcus serotyping was not performed. Third, it was a hospital-based study with small sample size.

Conclusions

CM is rare in Qatar and affects both HIV-positive and HIV-negative expatriates. Clinical presentations are nonspecific and require a high index of suspicion. Hence, it is essential to consider the possibility of CM during the investigation of all persons, including non-HIV patients, who present with chronic headache, especially in the presence of fever and neurologic deficits.

Authors' contributions

All authors were involved in the conception, conduct, and analysis of the study. They all participated in drafting and further development of the manuscript and approval of its final version.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

Ethical approval was obtained from the medical research committee at Hamad Medical Corporation. The study was a retrospective data examination exercise, however, all patients admitted to HMC do sign a general consent for anonymous use of anonymized data for quality assurance, education, and research that is deemed to cover the type of this study.

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