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Prevalence, risk factors and outcome associated with cryptococcal meningitis in HIV positive patients in Algeria: case series and review of literature

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ABSTRACT:

— ***Background:*** Cryptococcal meningitis is a severe fungal infection of the central nervous system associated with significant morbidity and mortality among people living with HIV/AIDS (PLWHA). This study aims at determining the prevalence, epidemiological characteristics, clinical features, neuroimaging, laboratory findings, and treatment, among PLWHA having CM and identifying early predictors of outcome.

— ***Case Presentation:*** We retrospectively analyzed data from 11 PLWHA with CM hospitalized in Setif hospital from January 1985 to May 2022. Eight men (72.7%) and three women (27.3%) were involved in the study; the median age was 39.27 years (range: 18-69 years); clinical manifestations included headache (9, 81.8%), fever (7, 63.6%), restless (6, 54.5%), seizure (3, 27.3%), meningeal syndrome (5, 45.5%); CD4 count ≤ 50 cells/mm^3 was detected in 6 patients (54.5%), 7 patients (63.6%) showed normal cerebrospinal fluid cell counts and 9 (81.8%) had a normal biochemical examination; 3 patients (27.3%) had abnormalities shown on intracranial imaging; 11 cases (100%) were culture positive, 10 (90.9%) were positive by India ink preparation, and in-hospital mortality was detected in 7 patients (63.6%).

— ***Conclusions:*** The study reports a low prevalence of CM among PLWHA attending our hospital and a high mortality despite the administration of Amphotericin b deoxycholate or Fluconazole. Factors as late presentation of patients, the lack of CrAg screening and the absence of Flucytosine may have contributed to the poor outcome.

— ***Keywords:*** *Cryptococcal meningitis, AIDS, Outcome, Mortality, Prognosis.*

INTRODUCTION

Cryptococcosis is a worldwide ubiquitous mycosis and a main factor of meningitis in persons living with HIV/AIDS (PLWHA), it is caused by members of the *C. neoformans* genus. In individuals with late-stage HIV infection, cryptococcal meningitis (CM) is a frequent opportunistic infection (OI) and AIDS-defining condition, generated from inhalation of fungal propagules, which can be accumulated in the pulmonary alveoli and has a remarkable proclivity to infiltrate the central nervous system (CNS); *C. gattii* complex neoformans is the most widespread cause of mortality among PLWHA with meningitis[1].

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CM constitutes a severe infectious illness of the CNS, despite breakthroughs in diagnostic and treatment approaches; regardless of the existence of efficient therapy, its lethality in poor, medium, and high-income countries has fluctuated from 10% to 43%[2], and it represents the second highest cause of HIV-related death globally, with the largest happening in Sub-Saharan Africa[1].

In order to avoid the onset of invasive cryptococcal illness, the World Health Organization (WHO) advises cryptococcal antigen (CrAg) screening among ART-naive adults and adolescents who are initiating care and have CD4 level below 100 cells/mm^3.

The antifungal therapy for HIV patients is divided into three phases: induction, consolidation, and maintenance, and is built on Amphotericin b deoxycholate (AmBd) and 5-flucytosine (5FC), followed by one week of Fluconazole (FCZ)[3].

This case series study is focused on the epidemiological, clinical manifestations, biological, neuroimaging features, treatment used, and outcome of CM in 11 patients with AIDS and provides a rare description of CM at a public hospital in Algeria over 36 years.

CASE PRESENTATION

Study Population

We retrospectively reviewed the clinical manifestations, biological, neuroimaging features, treatment used, and outcome of 11 adult patients, confirmed positive by Western blotting for HIV, diagnosed with cryptococcal meningitis, during a study period of 37 years (January 1985-May 2022), admitted to Saadna Abdennour Sétif teaching hospital in Algeria. Among 836 PLWHA, case records of patients with cryptococcal meningitis were chosen for the research. The isolation of *C. neoformans* in cerebrospinal fluid (CSF) cultures and/or positive CSF India ink stains was employed to diagnose cryptococcal meningitis.

Data Collection

Demographic, clinical, biological and neuroimaging data, treatment used, and outcome were obtained from medical records. The variables evaluated included sex, age, symptoms at admission, anti-fungal therapy, CD4 values, laboratory tests of cerebrospinal fluid (CSF) including glucose and protein dosage, white blood cell (WBC) count, culture, India ink test, results of neuroimaging (brain computerized tomography (CT) and/or Magnetic resonance imaging (MRI), duration of hospital stay, type of treatment and outcome. During the induction phase, patients received an intravenous infusion of standard AmBd, the only Amphotericin B preparation accessible in our institution; in the absence of AmBd, FCZ was utilized.

Demographic and Clinical Features

11 cases of cryptococcal meningitis were identified during the study period, among 836 PLWHA. The prevalence of CM was 1.3%, patients ranged in age from 18 to 69, with a mean age of 39.27; among those, 63.6% were under the age of 40, 72.7% were men, and 81.8% were heterosexual (Table 1).

In 7 individuals (63.6%), cryptococcal meningitis was the first sickness to occur, while 4 patients (36.4%) developed CM on anti-retroviral treatment (ART) – of these, 2 had unmasking of cryptococcal meningitis and 2 patients defaulted ART with clinical failure. The most frequent first symptom of cryptococcal meningitis in patients was a headache (81.8%), followed by fever (63.6%), and restlessness (54.5%). 9 patients (81.8%) had a Glasgow coma scale higher than 13; focal deficit was found in one patient (9.1%) and 3 patients (27.3%) had seizures; only 5 patients (45.5%) had meningeal syndrome at disease onset.

CD4 Value and CSF Finding

54.5% of the population had a CD4 count lower than 50 cells/mm^3, the median CD4 level being 59.18 cells/mm^3 (30-100). The WBC count for the CSF data varied from 0 to 238 (mean = 42.81); 8 (72.7%) had normal CSF WBC count and 9 (81.8%) showed a normal biochemical examination (Table 2). 100% of patients had CSF cultures that were positive for *C. neoformans*, and 90% had CSF samples that were positive for Indian ink staining.

Radiological Features

With regards to neuroimaging, cranial CT was performed in 10 patients (90.9%), while brain MRI was performed in 4 (36.4%); hydrocephalus was the most common (3 cases, 27.3%) while 8 patients had a normal result (Table 2).

Treatment of AIDS and CM was based on the Algerian Guidelines on HIV/AIDS Diagnosis and Treatment[4,5] built on AMBd in 7 cases (63.6%) and FCZ in 4 patients (36.4%) (Table 2).

Hospital death occurred in 7 patients (63.6%); patients remained hospitalized between 15 and 150 days with 62 days on average, till death; treatment was successful in 1 of the 7 patients assigned to AMBd as compared with 3 of the 4 assigned to Fluconazole (Table 2).

DISCUSSION

From the 1980s, the majority of CM cases have been seen in HIV/AIDS patients who had advanced immunosuppression, as indicated by a CD4 cell count lower than 100 cells/mm^3. The majority of them either did not take antiretroviral medication (ART) or had poor adherence[2]. Although diagnostic and treatment methods have improved, CM still has a high rate of morbidity and death. Globally, this opportunistic infection generates an estimated of 181,100 AIDS-related deaths per year, representing about 15% of all losses[1].

Even if timely use of antifungal therapy is known to be successful, several additional variables, as clinical and laboratory findings, are recognized[6,7] to have a significant effect on the outcome. We report our experience over 37 years, on clinical manifestations, biological, neuroimaging features, treatment regimens used and outcome among 11 hospitalized CM PLWHA.

Table 1. Demographics and clinical profile of patients.

Case	Year of diagnosis	Age at diagnosis	Gender	Population type	Marital status	HIV transmission	ART status	Signs and symptoms at admission	Glasgow coma scale	Meningeal syndrome
1	2001	42	F	Heterosexual	Married	Sexual contact	Naïve	Fever Headache	14	Present
2	2002	32	F	Heterosexual	Married	Sexual contact	Naïve	Fever Headache Restless Cranial paired paralysis	14	Present
3	2005	69	M	Heterosexual	Married	Sexual contact	Naive	Fever Headache Restless	14	Absent
4	2005	65	M	Heterosexual	Married	Sexual contact	Naive	Fever	14	Absent
5	2011	44	M	Heterosexual	Married	Sexual contact	Naive	Fever Restless	12	Absent
6	2010	26	M	Heterosexual	Single	Sexual contact	Poor adherence to ART (Viral failure)	Fever Headache	15	Absent
7	2013	32	M	Heterosexual	Single	Sexual contact	Poor adherence to ART (Viral failure)	Headache	15	Absent
8	2014	30	M	Heterosexual	Single	Sexual contact	SRIS	Seizure Headache	15	Absent
9	2016	18	F	Heterosexual	Single	Sexual contact	SRIS	Seizure Headache Restless	14	Present
10	2016	30	M	MSM	Single	Sexual contact	Naive	Seizure Headache Restless	15	Present
11	2020	38	M	MSM	Single	Sexual contact	Naive	Fever Headache Restless	13	Present

MSM, Men who have sex with men; M, Male; F, Female.

Table 2. Laboratory, radiological findings, treatment regimens and outcome of patients.

Case	CD4 Cells/µL	CSF aspect/ white Cells/mm^3	CSF Protein	CSF glucose	Neuroimaging	Cryptococcal	Treatment	Outcome
1	47	Clear 12	Increased	Decreased	Normal CT	CSF India ink preparation positive CSF culture positive	AmBd	Death 20 days into treatment
2	95	Clear 0	Normal	Normal	Normal CT	CSF India ink preparation positive CSF culture positive	AmBd	Death 40 days into treatment
3	58	Clear 2	Normal	Normal	CT: Hydrocephalus	CSF India ink preparation positive CSF culture positive	AmBd	Death 150 days into treatment
4	83	Clear 0	Normal	Normal	Not done	CSF India ink preparation positive CSF culture positive	AmBd	Death 29 days into treatment
5	40	Clear 2	Normal	Normal	CT normal MRI normal	CSF India ink preparation positive CSF culture positive	AmBd	Death 15 days into treatment
6	40	Clear 10	Normal	Decreased	CT normal	CSF India ink preparation positive CSF culture positive	AmBd	Alive at discharge
7	30	Clear 2	Normal	Normal	CT normal	CSF India ink preparation negative CSF culture positive	FCZ	Alive at discharge
8	58	Clear 200	Normal	Normal	CT: hydrocephalus, maxillary and ethmoidal sinusitis MRI: longitudinal sinus thrombophlebitis	CSF India ink preparation positive CSF culture positive	FCZ	Alive at discharge
9	50	Clear 0	Normal	Normal	CT/MRI: hydrocephalus	CSF India ink preparation positive CSF culture positive	AmBd	alive at discharge
10	50	Clear 0	Normal	Normal	CT/MRI: maxillary sinusitis	CSF India ink preparation positive CSF culture positive	FCZ	Death 3 months into treatment
11	100	Clear 238	Increased	normal	CT normal	CSF India ink preparation positive CSF culture positive	FCZ	Alive at discharge

CSF, cerebrospinal fluid; AmBd, Amphotericin b deoxycholate; FCZ, Fluconazole; CT, computerized tomography; MRI, Magnetic resonance imaging.

The first case of AIDS in Algeria was reported[8] in 1985, while at the end of 2019, there were 13,000 reported PLWHA, corresponding to a prevalence of approximately 0.1%. Despite having a "test and treat" (TAT) program currently in place in Algeria, whereby everyone proven to be HIV-positive is instantly started on ART, the issue of OIs including CM persists. Similar to the current study, the majority of publications[9,10] on CM in PLWHA patients found that this opportunistic infection mostly affected ART-naive individuals with low CD4 T cell baseline levels, whose CM was their initial AIDS-defining disease.

Male gender is thought to increase the likelihood of developing cryptococcosis in humans, and male patients tend to have worse prognoses. Nevertheless, the reasons behind this are still unclear. We noted a higher proportion of men as reported[11,12] by the majority of the studies. We observed that patients over the age of 40 have a worse prognosis, and comparable findings[13,14] have been previously published in literature.

Headache, fever and restless were the important presenting symptoms of cryptococcal meningitis in our series, similar to earlier reports[15,16] in the literature.

CM neuroimaging can be normal or detect brain oedema, hydrocephalus meningeal thickening, single or many cryptococcomas. In our study, 72.7% of CT was normal and 27.3% revealed hydrocephalus.

Due to the immunocompromised status, CSF showed a lower inflammatory response leading to lower white cell counts in HIV-infected patients[17]. CSF WBC counts lower than 5/mm^3 have been linked[13,18] to a poor prognosis, but these values did not appear to alter the outcome of our patients.

Cryptococcal meningitis can be diagnosed using CSF culture, India ink, or Cryptococcal antigen (CrAg) testing. The gold standard for diagnosing cryptococcal meningitis is CSF culture. Unfortunately, diagnosis might take several days, and final findings usually take up to two weeks. India ink microscopy is a rapid and low-cost approach for detecting *Cryptococcus* in CSF[19]; however, sensitivity is low (86%)[20]. Latex agglutination may detect CrAg with both high specificity and sensitivity of more than 99% in blood and CSF[20].

CSF culture was positive in all our patients; positive India ink preparation had been found in previous studies[18,21] to be a major disadvantageous prognostic factor. Crag was not available at the moment of the current study. CrAg screening is indicated for ART-naive HIV-infected people with a CD4 count < 100 cells/mm^3 prior to ART in order to detect and treat latent infection before immune reconstitution finally reveals it[3]. Fluconazole primary prophylaxis should be provided to people living with HIV who have a CD4 cell count < 100 cells/mm^3 when cryptococcal antigen testing is not accessible[3].

In our country, CrAg screening among ART-naive HIV-infected patients with a CD4 count <100 cells/mm^3 is not performed because it is not recommended in the national guideline[5], while the TAT program has frequently resulted in the introduction of ART prior to the CD4 count and without CrAg screening.

The approved CM therapy for HIV patients is divided into three steps: induction, consolidation, and maintenance. In resource-limited settings, the WHO modified worldwide guidelines in 2018 to promote induction treatment with a 1-week regimen of AmBd and Flucytosine[3]. Despite the fact that one week of AmBd therapy is associated with anemia, renal dysfunction, and electrolyte disorders[22], adding Flucytosine results in faster sterilization of the CSF and fewer relapses than with the use of AmBd alone[23].

As alternative options depending on drug availability, the following induction regimens are recommended: two weeks of Fluconazole + Flucytosine or two weeks of AmBd + Fluconazole.

Since it can be administered at larger dosages with less drug-induced adverse effects, and does have a long tissue half-life, with efficiently penetrates brain tissue, liposomal Amphotericin B could be perfectly adapted to be used in short-course induction treatments of cryptococcal meningitis[24].

Induction therapy with a single 10 mg/kg dosage of liposomal Amphotericin B in conjunction with 2-week Flucytosine plus Fluconazole demonstrated non-inferiority and tolerance advantages to WHO recommended induction therapy, according to Jarvis et al[25].

When this study was being conducted, Algerian guidelines[4] for the treatment of CM advised using Amphotericin B monotherapy for two weeks, followed by an eight-week consolidation period with Fluconazole monotherapy. Thereafter, oral prophylaxis with this medication was continued until their immune systems recovered. The new Algerian clinical guidelines[5] added the use of liposomal Amphotericin B while maintaining others drugs cited above. However, at the time of study, lipid formulations of Amphotericin B and Flucytosine were not available in Algeria's public health services.

Death rates keep rising, varying between 20% and 60% with therapy and up to 100% without[26,27]; in this case series, a significant mortality rate (63.6%) was seen, particularly among patients treated with AmBd.

Despite wider availability of free ART, Algeria still has several late presenters; all our patients had CD4 < 100 cells/mm^3, and were at high risk for developing CM, hence primary prophylaxis or CrAg screening should be used as a first defense strategy.

CONCLUSIONS

The study reports a low prevalence of CM among PLWHA attending our hospital and a high mortality despite the administration of Amphotericin b deoxycholate or Fluconazole. Factors as late presentation of patients, the lack of CrAg screening and the absence of Flucytosine may have contributed to the poor outcome.

These results underscore the importance of having access to optimal drugs for the treatment and tools for early diagnosis to permit primary prophylaxis.

Conflict of interest:
The authors declare no conflicts of interest.

Ethics Approval:
By ensuring the patients' safety and confidentiality, this study has been done in strict accordance with ethical standards. The study team alone retained and amended the gathered data. The study was approved by the research Ethical Committee of University Ferhat Abbes Setif, Algeria.

Informed Consent:
All participants gave their consent before data were collected.

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