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Original Article

Clinical Profile and Disease Outcome of Cryotococcal Meningitis in Patients with HIV/AIDS Infection: A Prospective Study at Tertiary Care Centre in North India

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Abstract

Background: *Cryptococcus neoformans is the common opportunistic infections (OI), in people living with HIV/AIDS (PLHA) and cryptococcal meningitis (CM) the main clinical manifestation adds to morbidity and mortality, 10-30%. Management includes concurrent treatment of HIV infection and specific management of cryptococcal meningitis, potent fungicidal drugs include amphotericin and flucytosine, though flucytosine is not available in limited resource settings, fluconazole is used as alternative.*

Objectives: *To study the clinical profile and disease outcome of cryptococcal meningitis in patients living with HIV/AIDS infection (PLHA).*

Material and Methods: *An prospective study from a tertiary care centre at Northern India. Patients with HIV/AIDS infection (PLHA) presenting with signs and symptoms of CNS infection, diagnosed as cases of cryptococcal meningitis (CM) were evaluated and respective data collected.*

Results: *Twenty three with HIV/AIDS infection were diagnosed as cases of CM and evaluated. 16(69%) presents with CM as AIDS defining illness. Common clinical features included Headache (90%), fever (80%), followed by vomiting and altered sensorium. CD4 count <100 was significantly associated with CM. On CSF analysis cryptococcal Ag was +ve in 23 and India ink tested +ve in 16 patients. On neuro imaging meningeal enhancement was the commonest finding followed by localized ring shaped lesions, hydrocephalus and infarct.*

Conclusion: *The disease burden is more in developing and underdeveloped nations with high incidence of human immunodeficiency virus infection. Individuals infected with HIV infection may develop CM in course of HIV disease or may present with cryptococcal meningitis as AIDS defining illness. High degree of clinical suspicion and timely induction of treatment is associated with better outcomes.*

Introduction

Cryptococcosis an infectious disease prevalent globally with varied clinical presentation. People living with HIV/AIDS (PLHA) are at higher risk besides people on immuno-suppression as organ transplant hosts, although at times

immunocompetent host is also affected commonest clinical presentation being cryptococcal meningitis (CM).[1,2] Though the incidence of CM has declined in developed countries still it constitutes common and important OI in PLHA in developing and under developed Nations. In PLHA most common clinical manifestation is meningitis and presentation can be acute, sub acute or chronic and sometimes initial clinical signs and symptoms are similar to the meningitis due to other infections as tubercular, so early diagnosis and induction of treatment is associated with better outcomes.CM presents as AIDS defining illness in 60% of people infected with HIV/AIDS and adds to morbidity and mortality (30%).[3,4] This study describes the clinical presentation and disease outcome of patients with HIV/AIDS and concurrent cryptococcal meningitis.

Material and Methods

This prospective cohort study was conducted at Government Medical College, Jammu, a tertiary care centre in northern India, over a period of one year, after getting approved by Institutional Review Board and Ethical Committee. The subjects under study included HIV-positive cases, already on antiretroviral treatment (ART) and, those who presented with cryptococcal meningitis as AIDS defining illness. Patients having clinical features of meningitis and CSF positive for cryptococcal Ag and India ink test were considered as case of CM. Patients with other OI , pretreatment hemoglobin <10 gram, liver dysfunction, renal dysfunction, diabetes mellitus, impaired fasting blood serum level and patients with age <18 years were excluded from the study.

Total of 23 patients were included in the present study subjects were included in the study, patients presenting with clinical signs and symptoms of meningitis, cryptococcal infection as cause of CNS infection was confirmed by, cryptococcal antigen positivity, India ink staining and biochemical and cytological analysis of CSF. A detailed history of every patient was taken including past history of ART, history of fever, cough, breathlessness, past or present history of opportunistic infections *i.e.*, pulmonary / extra pulmonary tuberculosis, skin lesions, mucosal lesions and sexually transmitted diseases (STD). Clinical presentation including symptoms and signs, laboratory parameters, CSF findings, imaging, treatment outcomes, adverse drug reactions were analyzed. Amphotericin 0.7mg/kg/D along with Fluconazole 800mg /D for 2 weeks followed by fluconazole 400 mg for next 8 weeks and subsequently put on fluconazole prophylaxis 200mg/D. The statistical analysis of data collected was done by appropriate statistical method.

Results

In the present study, subjects under study included 23 HIV-positive cases diagnosed as cases of cryptococcal meningitis, 14 male and 9 female. Three patients died during the study period .Male predominance with male female ratio of 1.55 was observed. Most patients were below age <35yrs. CM as AIDS defining illness was seen in 16(60%), rest were on ART for varied time period (Table 1). Common presenting symptom was head ache (90%), followed by vomiting .Fever presented in 80% of patients characteristically low grade pattern was seen. Seizures (40%), Altered sensorium (10%), motor deficits (10%) were other presenting symptoms.CD4 count varied from 50 to 150 cells /umm. Adverse drug reactions observed were hypokalemia, rashes, fever and renal dysfunction mainly attributed to Amphotericin and paradoxical immune reconstitution inflammatory syndrome (IRIS) in 20% (Table 2)

Table 1: Characteristics of the patients enrolled

Characteristics	Number of patients (%) (n = 23)
Gender	
Male	60%(14)
Female	40%(9)
Age in years	
< 35	69%(16)
> 35	31%(7)
CD4+ T-cell counts at presentation	
< 100	74%(17)
> 100	26%(6)
ART status	
Patient on HAART	31%(7)
Cryptococcal meningitis as AIDS defining illness	69%(16)
ART regimen	
Death	13%(3)
Others (Amphotericin B 0.7 mg/kg/day)	100%(23)
Fluconazole 800 mg/day	100%(23)

Table 2: Characteristics of the patients enrolled

Characteristics	Number of patients (%) (n = 23)
Symptoms / signs	
Headache	90%(20)
Fever	80%(18)
Vomiting	60%(14)
Seizure	40%(9)
Altered sensorium	21%(5)
Focal neurodeficit	10%(2)
CSF studies	
No. of cells (5-20)	65%(15)
No. of cells> 20	35%(8)
Cryptococcal antigen	100%(23)
India ink	69%(16)
Imaging (CT/MRI)	
Normal	17%(4)
Focal lesion	26%(6)
Meningeal enhancement	35%(8)
Hydrocephalous	13%(3)
Adverse drug reactions	
Hypokalemia	21%(5)
Fever	21%(5)
Rashes	13%(3)
Renal dysfunction	13%(3)
IRIS	21%(5)

Discussion

The pandemic of HIV/AIDS is associated with increased incidence of cryptococcal meningitis and constitutes the most common opportunistic infection. Availability and access to HARRT has contained the infection as such, however poor adherence and associated comorbidities pose a constant threat and predisposition to cryptococcal infection. People living with HIV/AIDS are at increased risk of cryptococcosis when CD4 count falls below 1 was <100cells/µml. Cryptococcal meningitis has been reported as the common opportunistic infection of central nervous system (CNS) in PLHA in India.[2,6] This infection is fatal without treatment.

The clinical presentation poses challenge as not being different from other causes of meningitis. Main presenting features include fever headache,

confusion and increased intracranial pressure associated with seizures and cranial nerve palsies. Classical presentation of meningism in seen in about 20% of cases and increased mortality is seen in patients with altered mental state.[3,5]

Diagnostic modalities include high degree of clinical suspicion, CSF analysis and imaging studies. Cryptococcal antigen, India ink staining, biochemical analysis and cytology also equally important. In our study fever, confusion and seizures were the main presenting features and in 6 patients was the initial presentation of HIV/AIDS. In 16 patients (80%), CD4 count was <100cells/µml, various studies have reported cell count of <100/µml in majority of PLHA with CM. CSF analysis in our study revealed cell count <20 cells/cuml with lymphocytic predominance consistent with various studies as reported. The low cell count is attributed to suppressed immune response to cryptococcus in PLHA reason being impaired cell mediated immunity. In our study India ink positivity was reported in 80% of patients and is attributed to high pathogen burden due to impaired immunity. Rapid diagnosis of CM is done by detection of Cryptococcus in CSF, India ink method being easy and simple modality for diagnosis, sometimes lymphocytes, tissue cells and nonyeast forms can lead to false +ve results. Latex agglutination test (LAT) has improved the diagnosis of CM, utilizing CrAg (cryptococcal capsular polysaccharide Ag), and has got sensitivity and specificity of 93-100% and 93-98% respectively. In our study LAT was +ve in 23 patients. Imaging studies including CEECT and MRI usually present as meningeal enhancement, focal lesions as infarct, crytococcomas and hydrocephalus.[1,2]

The management also poses a challenge, though amphotericin along with flucytosine is recommended, but nonavaliability of flucytosine and its high cost is the limiting factor in some settings and at times adverse drug reactions also pose a challenge.[5,8]

In our settings, amphotericin B and fluconazole was mainstay of treatment, although recommended treatment being combination of amphotericin B and flucytosine for the initial two weeks. In our study, we used amphotericin B (0.7 mg/kg/day), minimum for two weeks. Flucytosine was not used because of its non-availability. The main adverse drug reaction observed with amphotericin was hypokalemia (6/10 patients; 20%) and is attributed to renal tubular dysfunction due to amphotericin, followed by fever (3/10 patients; 20%), rashes and deranged renal function (serum creatinine >2 mg%) in 2 person (10%) each.[1,8] All patients were managed conservatively. Anemia was seen in two patients and attributed to zidovudine. Amphotericin B use is associated with multiple adverse drug reactions as electrolyte imbalance, nephrotoxicity, anemia and infusion reactions. Renal function, serum electrolytes and complete blood count monitoring is recommended with Amphotericin B use, proper fluid management with electrolyte supplementation is associated with better outcomes. Liposomal amphotricin B or lipid complex preparation of amphotericin B are recommended in high risk patients. Concomitant use with nephrotoxic drugs as tenofovir should be monitored closely and if renal toxicity observed dose modification of tenofovir is recommended. Anemia is usually transient however additive suppression of bone marrow is seen with concomitant zidovudine use. IRIS was observed in 20% of patients characterized by worsening of neurological status and altered sensorium, headache and signs of raised intracranial tension (ICT) were the main clinical features. IRIS is mainly classified into Paradoxical IRIS characterized by deterioration of clinical signs and symptoms after initial improvement and unmasked IRIS in which there is deterioration of preexisting illness following initiation of HARRT. Incidence of paradoxical IRIS reported in literature varies between 8-49%. It is diagnosis of exclusion, manifestations include relapsing aseptic meningitis, increased ICP, intracranial cryptococcomas/abscess, focal neurological deficits and multifocal disease. Management includes continuation of ART and

antifungal agents. Symptomatic management for mild form and for more severe corticosteroids NSAIDS, and immunomodulators as thalidomide, hydroxychloroquine and adalimumab have been successfully used.[1,2,8]

Conclusion

Cryptococcal meningitis continues to be common and potentially lethal opportunistic infection in PLHA. The present study demonstrated the prevalence of CM in PLHA the main presentation was acute to subacute.CM continues to be common OI in PLHA and AIDS defining illness. Patients with CD4 count <100/mml continues to be at high risk. High degree of clinical suspicion and timely CSF analysis is associated with early diagnosis and better clinical outcome.

References

1. Badave RR, Gaswaraj A. Clinical profile of cryptococcal meningitis in patients living with HIV infection: an experience from Western India. DY Patil Vidyapeeth 2019.
2. Naik KR, Gokarappa A, Doshi DK. Hospital based retrospective study of cryptococcal meningitis in a large cohort from India. Ann Indian Acad Neurol 2017;20:225-8.
3. Mahale M, Patil S, Ravikumar, Nagabhushan, Mahale R. Prevalence of cryptococcal meningitis among immunocompetent and immunocompromised individuals in Bellary, South India –a prospective study. J Clin Diag Res 2012;388-92.
4. Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2016;30:179-206.
5. Sloan DJ, Parris V. Cryptococcal meningitis: epidemiology and therapeutic options. Clin Epidemiol 2014;6:169-82.
6. Kumar S, Wanchu A, Chakrabarti A, et al. Cryptococcal meningitis in HIV infected: Experience from a North Indian tertiary center. Neurol India 2008; 56: 444-449.
7. Kambugu A, Meya DB, Rhein J et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therpay. Clin Infect Dis 2008; 46 : 1694-1701.
8. Srichatrapimuk S, Sungkanuparph S. Integrated therapy for HIV and cryptococcosis. AIDS Res Ther 2016;13:42.