Cryptococcal Meningitis: Looking beyond HIV

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Abstract- Introduction: Cryptococcal meningitis is a type of meningitis. It has conventionally associated with HIV infection. However, few cases are also described in patients with other forms of immunosuppression and in apparently immunocompetent individuals as well. Objectives: We reviewed 15 cases hospitalized and diagnosed with cryptococcal meningitis at Kasturba Hospital, Manipal in the last two years. We also compared the clinicopathologic characteristics of meningitis in HIV positive and HIV negative groups. Results: 9 of 15 patients with cryptococcal meningitis had been diagnosed with HIV, remaining 6 were HIV negative. The predominant clinical features in both groups were headache, vomiting and fever. The patients with HIV had the following features: more acute onset of signs and symptoms a higher mortality rate, low to normal leucocyte count with a predominance of neutrophils and an initial high cryptococcal antigen titre. The CSF glucose was low whereas the protein was elevated. The HIV negative group had a late onset of illness, higher leucocyte count with a predominance of lymphocytes and lower cryptococcal antigen titre. The CSF glucose and protein were normal. Conclusion: Both groups had a well-defined set of characteristics which could be useful in diagnosing and predicting the course of the disease.

Index Terms- Cryptococcus, meningitis, immunosuppression

I. Introduction

Cryptococcus neoformans is an encapsulated yeast. The incidence and prevalence of this pathogen has risen exponentially over the past two decades; parallel with the rise of HIV and with an ever increasing use of immunosuppressive therapies.[1] Cryptococcal meningitis is a common opportunistic infection and AIDS-defining illness in patients with late-stage HIV infection.[1,2] Cryptococcal meningitis also occurs in patients with other forms of immunosuppression and in apparently immunocompetent individuals as well. Mortality from HIV associated cryptococcal meningitis remains high in many countries due to multiple factors. Some of them include the insufficiency of antifungal drugs, and the complications such as raised intracranial pressure.[3,4] Since the data on the clinical characteristics and prognosis of cryptococcal meningitis in HIV positive and HIV negative patients is limited, we reviewed 15 cases diagnosed in a major tertiary care hospital in Karnataka.

II. Objectives

1. To review the cases diagnosed as cryptococcal meningitis in HIV positive and HIV negative patients and study their clinicopathologic profile.
2. To ascertain any distinguishing features between the 2 groups.

III. Materials and Methods

It was retrospective study of 15 cases, hospitalized and diagnosed as cryptococcal meningitis, over the last 2 years (2010-2012) at Kasturba Hospital, Manipal. An approval from the Institutional Ethics Committee, Kasturba Hospital, Manipal was obtained before the study. The clinical data was obtained by reviewing the medical records of the patients. For patients with meningitis, cerebrospinal fluid (CSF) was routinely sent for complete white blood cell (WBC) counts and differential counts, glucose, protein and culture. CSF testing with India ink was also performed. The titres of antibody against cryptococcus species were obtained by enzyme immunoassay technique.

IV. Results

The results of the clinical features at the time of presentation are shown in table 1. The median age for HIV group had a younger profile (27.4 years). The most common presenting features were fever, headache and nausea/ vomiting. 7 of 9 patients had features of meningism. The duration of symptoms was approximately 10 days. 5 patients had hydrocephalus, requiring a ventriculo-peritoneal shunt (VP shunt) to lower the intracranial pressure. Significantly, 4 patients succumbed to the disease.

The median age for HIV negative group had a relatively older profile (45.2 years). The common presenting features were similar to HIV positive group; although not as prevalent. The duration of symptoms was longer (17.6 days). Though 2 patients had hydrocephalus, neither required a ventriculo-peritoneal shunt (VP shunt). Significantly, this group had no mortality due to the disease.

Table 1: Comparison of the clinical profiles of cryptococcal meningitis in HIV positive and negative group

Clinical features	HIV positive group (n=9)	HIV negative group (n=6)
Median age	27.4 years	45.2 years
Signs& symptoms		
a. Fever	100%	100%
b. Headache	88.8%	66.7%
c. Nausea/ vomiting	55.5%	50%
d. Altered sensorium	44.4 %	16.7%
e. Meningeal signs	77.7%	50%
f. Seizures	33%	16.7%
g. Duration of onset of symptoms(days)	10	17.6
Hydrocephalus	55.5%	33%
Death due to disease	44.4%	-

The CSF examination parameters for the two groups are listed in table 2. The HIV positive group had a lower total leucocyte count (23 cells/mm^3) with a predominance of neutrophils. Plasma cells were invariably noted in the differential count. The glucose levels were within normal range whereas the protein was raised. This group had a high antigen titre (>1:256).

In stark comparison, the HIV negative group had a significant leucocytosis (96.3 cells/mm^3) with lymphocyte predominance. The eosinophils were relatively more compared to the first group. The CSF protein and glucose concentration were within normal range. The antigen titres were also low.

Table 2: Comparison of the CSF examination profiles of cryptococcal meningitis in HIV positive and negative group

CSF examination	HIV positive group (n=9)	HIV negative group (n=6)
Total WBC count (median)	23/cu.mm	96.3/cu.mm
Differential count (median %)		
a. Neutrophils	76.1	45.2
b. Lymphocytes	22.2	59.8
c. Eosinophil	3.1	9.2
d. Plasma cells	5.4	0.6
Glucose (mg/dL)	28	39
Protein (mg/dL)	65	42
Antigen titre	> 1:256	1:16

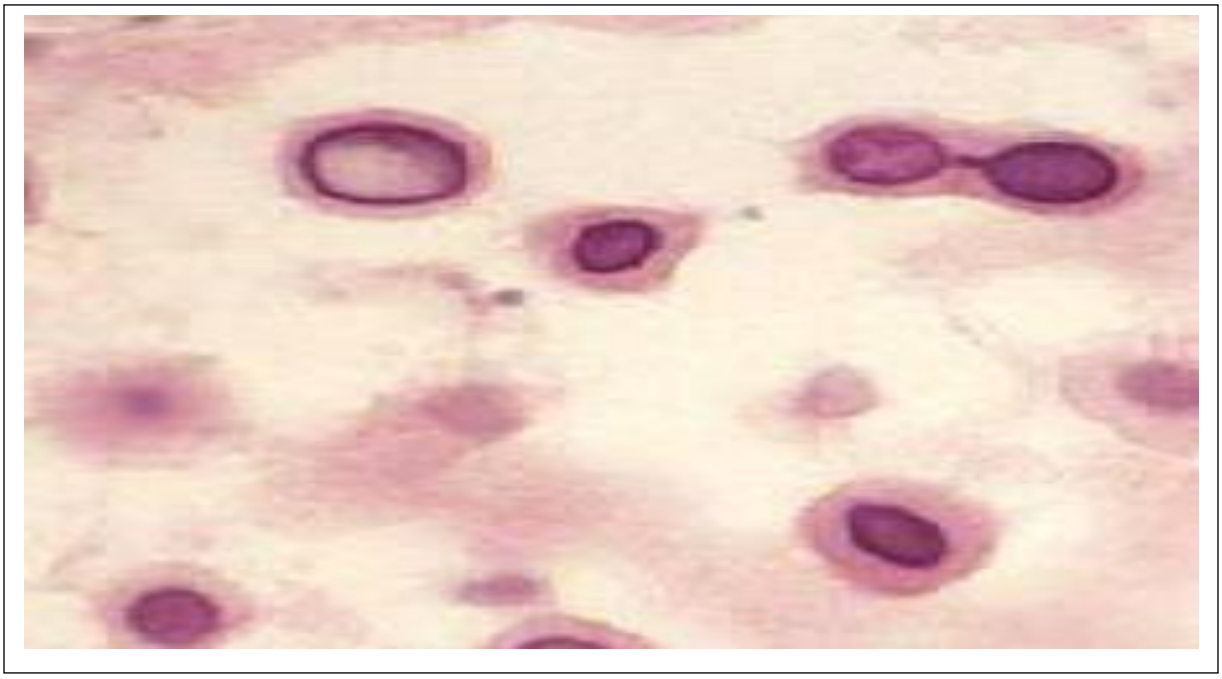

Figure 1: Cerebrospinal fluid showing budding, encapsulated yeast forms of *Cryptococcus neoformans* species. (Leishman ; x400)

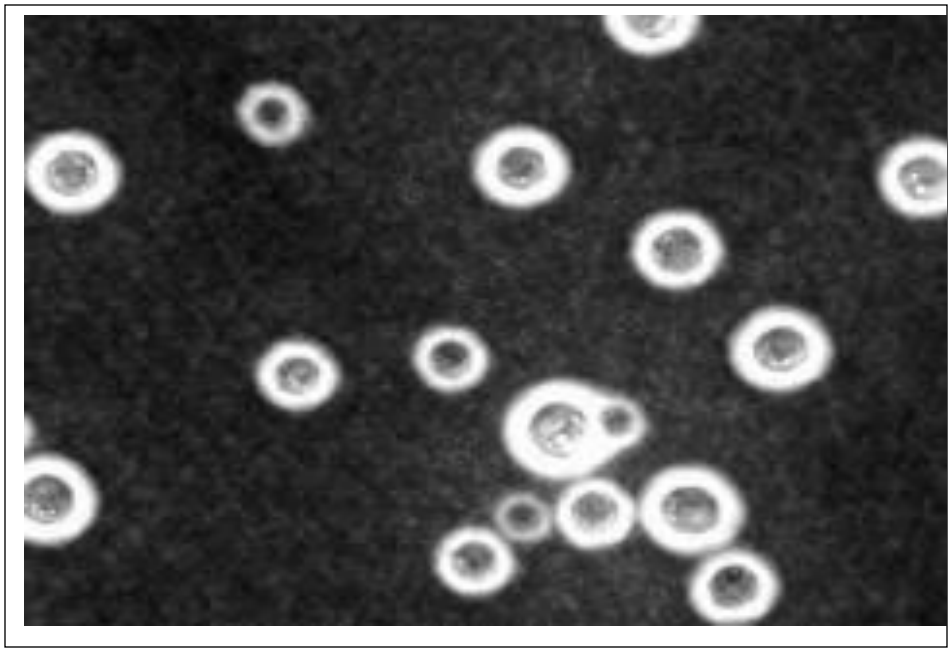

Figure 2: India ink preparation demonstrating the negative staining of Cryptococci. (India ink; x200)

V. Discussion

Cryptococcus neoformans is a saprophytic fungus. The infections in humans by this fungi is accidental. However, this basidiomycete fungi has evolved over a period of time. This has also enable it to survive in humans and other mammalian and avian hosts.[5,6] The incidence cryptococcal meningitis has risen in parallel to the HIV epidemic; particularly in the last two decades. Cryptococcal meningitis is also regarded as an AIDS-defining criteria in patients with late-stage HIV infection.[1,2] This however has also led to the overshadowing of the data on this disease in the non HIV cases. But with the ever-increasing use of immunosuppressive therapies, the incidence of cryptococcal meningitis in the non HIV group has been on the rise.[7]

In a large case series conducted by Pappas and co-workers[8], a total of 306 HIV-negative patients with cryptococcosis were studied. In the same study, the predisposing conditions included the long term usage of steroids (28%), post-organ transplant status (18%), chronic organ failure (liver, lung, kidney) (18%), neoplasia(18%) and rheumatologic disease (13%). A quarter of patients included in the study had no identifiable predisposing factors in the same series. In the present study, the 6 HIV-negative patients diagnosed with cryptococcal meningitis included 2 cases of chronic kidney disease on immunosuppressant drugs including steroids, 2 pediatric cases of acute lymphoblastic leukemia on antineoplastic chemotherapy regimen. The remaining 2 cases had no identifiable predisposing factors.

The main virulence factor that enables cryptococcus neoformans to survive and multiply in the human host is when T-cell immunity is jeopardized. The other inherent properties of the fungus include the ability to grow at room temperature, i.e. 37°C, the capsule, which enables it to resist phagocytosis by the macrophages. The same capsule is known to inactivate the cellular and humoral immune responses when shed into host tissues. Casadevall and colleagues had demonstrated that the fungi also possess laccase and melanin that interfere with oxidative killing by phagocytes.[5] Production of melanin from L-dopa by the enzyme laccase is also reported to be the main cause for the predilection of the organism for the central nervous system (CNS).[6]

Meningitis is regarded as the most common clinical manifestation of cryptococcosis.[6] Once the infection of the subarachnoid space is initiated, the involvement of the brain parenchyma usually frequent. In keeping with the conventional trend, the demographic of HIV positive patients with cryptococcal meningitis had a younger profile (median: 27.4 years) in our study. This was in sharp contrast to the non HIV group which had an older profile (median: 45.2 years). Patients with cryptococcal meningitis usually present with a diffuse headache, febrile status, generalized malaise and altered sensorium over several weeks. In our study, the most frequent symptom was fever, followed by headache and nausea/vomiting. There was no discrepancy with respect to this in both groups. Interestingly, this differed from the findings of C.C.Shih and colleagues, who found headache to the predominant symptom in the non HIV group.[7]

The HIV group had a more acute onset of clinical symptoms (median: 10 days) compared to the other group. Few research workers have recently found that T cell suppression in HIV negative population also had an acute onset of clinical features with a median of 14 days.[7] Additionally, the meningeal signs and complication such as altered sensorium, seizures and hydrocephalus was observed more in the HIV positive group as opposed to the non HIV group. This was also associated with a rise serum cryptococcal antigen titre and a scant CSF inflammatory response. These findings could be attributed to the impairment of immune response in HIV. Furthermore, these

characteristics concurred with the observations made by Bicanic and Harrison.[6] Significantly, 2 patients in the HIV-positive group succumbed to the illness and its complications. At the time of writing this article, the follow up available for 4 of the 6 HIV negative patients with cryptococcal meningitis has not shown mortality.

We observed that the CSF protein was higher for HIV positive patients (median: 68mg/dL) as opposed to HIV negative group (median: 42mg/dL). This finding was observed in other epidemiological studies on cryptococcosis as well.[6,9] Meanwhile, the CSF glucose levels were within normal range in both the groups. This characteristic differed from literature findings which places a low CSF glucose levels as a feature particular to HIV positive cryptococcal meningitis.[6,9-11]

With regard to the other laboratory findings, there was an interesting difference in the differential leucocyte count of the CSF. The HIV positive cryptococcal meningitis had a relative increase in polymorphs with fewer lymphocyte counts. More than occasional plasma cells were also noticed in the smears. In sharp contrast, the HIV negative group had mild lymphocytosis and few eosinophils. The former could be attributed to an impaired immune response while the latter could be a stronger immune reaction. The mild lymphocytosis was not observed in the CSF examination of the 2 HIV negative patients on immunosuppressants.

The India ink preparation demonstrates the capsule of C. neoformans. We observed that the HIV infected group had a stronger positive test than the other group. A negative India ink test on CSF is a good prognostic sign in HIV negative cryptococcal meningitis but does not seem to have the same implication in patients with AIDS.[12] The capsule of the fungus sheds specific antigens which can be detected in the CSF.[13] Surprisingly, the demonstration of antibodies to C. neoformans are seldom of any utility in the diagnosis of this condition. On the other hand, detection of the cryptococcal polysaccharide antigen in body fluids by latex agglutination tests or enzyme immunoassay has a better sensitivity and at a titre of >1:4, is considered very specific. High initial CSF titres are known to parallel a high organism burden by quantitative culture and indicate a poor prognosis.[11,14] In the present study, a higher antigen titre was seen in HIV positive group (median: >1:256) as opposed to the HIV negative group. A fall in the CSF antigen titres with the administration of antifungal drugs is noted. But this phenomenon is considered to be insignificant in the overall management of this disease.[11]

A glance into the recent literature on cryptococcal meningitis enlists the adverse prognostic factors. These include the presence of an underlying disease (malignancy or chronic steroid use), absence of headache, abnormal mentation status, high organism load demonstrated by a Indian ink positivity or a rise in the cryptococcal antigen titre, an insufficient host inflammatory response and raised CSF pressure.[15,16] Some of these variables were seen in the HIV positive patients in our study which could be culpable for the mortality of 2 cases. In a more recent series of cryptococcal meningitis in HIV negative patients, after the introduction of antifungal regimen, factors deciding mortality included chronic renal, liver failure, hematologic malignancy, absence of headache and altered mental status.[8] Although no patient succumbed to the disease in the HIV negative group, the risk factors were present in the 6 patients.

VI. Conclusions

The predominant clinical features in both groups were headache, vomiting and fever. The patients with HIV had the following features: more acute onset of signs and symptoms a higher mortality rate, low to normal leucocyte count with a predominance of neutrophils and an initial high cryptococcal antigen titre. The CSF glucose was low whereas the protein was elevated. The HIV negative group had a late onset of illness, higher leucocyte count with a predominance of lymphocytes and lower cryptococcal antigen titre. The CSF glucose and protein were normal. Thus, patients with HIV positive and HIV negative cryptococcal meningitis have distinct clinicopathologic features which could aid in diagnosis and predicting the course of the disease.

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