

Cryptococcal meningitis in non HIV immune compromised patients

K. SARKAR¹, S. KUMAR¹, B. SAHA¹, S. SARKAR², M. BESRA², R. SAHA²,
S. BHATTACHARYA³ AND S. BASAK³

¹ Department of Microbiology, School of Tropical Medicine, Kolkata

² Department of Dermatology, School of Tropical Medicine, Kolkata

³ Department of Microbiology, Mycology Division, School of Tropical Medicine, Kolkata

Received : 18.02.2013

Accepted : 06.06.2013

Published : 28.10.2013

This is a report of three cases of cryptococcal meningoencephalitis in 33 years old female, 72 years male and 42 year female, who were on immunosuppressive therapy. The variability of symptoms in non-HIV patient with cryptococcal meningoencephalitis poses diagnostic challenge and requires high level of suspicion to consider it as a differential diagnosis.

Key words: Meningoencephalitis, Cryptococcal antigen, Amphotericin B

INTRODUCTION

Cryptococcus neoformans, yeast like fungus, is the etiologic agent of cryptococcosis. The infection is acquired from the environment by inhalation of aerosolized infectious particles. Cryptococcosis occurs mostly in individuals with AIDS and other forms of impaired immunity (Harrison's Principles of Internal Medicine, 17th ed). Its distribution is worldwide. This infection may present with pulmonary infection- cough, chest pain and fever but generally present with meningitis or some other manifestation of extrapulmonary dissemination (Dupont, 1989). In patient with meningitis although headache and neck stiffness may not be severe, but other signs such as confusion, drowsiness, photophobia and cranial nerve palsies may be found (Manson's Tropical Diseases, 22nd Ed).

Observations

Case 1

A 33 year old female was diagnosed to be suffering from autoimmune hepatitis after relevant investigations and liver biopsy followed by histopatho-

logical examination. She was prescribed oral steroids in the form of prednisolone (30 mg /day) and tablet azathioprine (50 mg/day) to which she responded satisfactorily. She remained in follow up with gradually improving liver function tests and prednisolone was tapered to maintenance dose 10 mg/day in due course of follow up.

After 9 months of therapy she complaint intermittent mild grade fever along with mild global headache and without any other suggestive foci for 12-15 days. On physical examination mild grade pallor, icterus and hepato-splenomegaly was present. Her laboratory parameters were normal except for mild microcytic anaemia (Hb-10.9 gm% , MCV-73.2) and mildly elevated Bilirubin level (3.0 mg/dl) without much alteration of liver enzymes. Peripheral blood smear for malaria parasite was repeatedly negative. Blood and urine culture didn't show any growth. HIV ELISA was negative. Contrast enhanced CT scan of brain was normal. Lumbar puncture was done to encounter a high opening pressure and the CSF study revealed protein 61.3 mg/dl, glucose 13 mg/dl and cell count 13 cells/c.mm with lymphocytic predominance (96%). CSF Cryptococcal antigen (CRAG) was positive in 1:256 titre. The India Ink staining of CSF showed field studded with budding yeast cells and culture in

¹Email: dr.kumkum.sarkar@gmail.com

SDA medium showed growth. Amphotericin B was given at the dose of 0.7 mg /kg BW for 14 days under electrolytes and renal parameter monitoring. At the end of 14 days again CSF study was done and the India ink stain again showed the fields with budding yeast cell. Amphotericin B was extended in same dose for the next 14 days and a repeat CSF study showed presence of yeast cells but the number of yeast cells had decreased. Amphotericin B was further extended but the patient succumbed soon to the florid illness.

Case 2

A 72 year old male was diagnosed to be suffering from Pemphigous Foliacious after skin biopsy followed by histopathological examination. He was prescribed oral steroid- Prednisolone (40 mg/day) and tablet Azathioprine(50 mg/day) to which he responded satisfactorily.

After one year of therapy he presented with low grade fever along with global headache and without any other suggestive foci for 20 days. On physical examination he had pallor and mild neck rigidity. His laboratory parameters were normal and HIV ELISA was negative. Contrast enhanced CT scan of brain was normal. Lumbar puncture showed high opening pressure and the CSF study revealed protein 54 mg/dl, glucose 25 mg/dl and cell count of 40 cells/c.mm with lymphocytic predominance (86%). CSF cryptococcal antigen (CRAG) was positive in 1:128 titre and the India Ink staining showed field studded with budding yeast cells. Culture in SDA media showed growth. This patient was treated successfully with Amphotericin B.

Case 3

A 42 year female, known patient of SLE, was on immunosuppressant for 2 years, presented with mild fever, vomiting and behavioural abnormalities for 8 days. Her laboratory parameters and CT scan of brain were normal. HIV ELISA was negative and CD₄ count was 294 cells /c.mm. Lumbar puncture showed high opening pressure and the CSF study revealed protein 64 mg/dl, glucose 93 mg/dl, cell count 14 cells/c.mm with lymphocytic predominance (90%). CSF cryptococcal antigen (CRAG) was positive in 1:128 titres and the India Ink staining showed field studded with budding yeast cells. Culture confirmation of the aetiological agent was done. Patient was treated successfully with Amphotericin B.

DISCUSSION

Cases have been reported in the past about occurrence Cryptococcal meningoencephalitis in non-HIV cases of immunosuppression. Clinical presentation of cryptococcal meningoencephalitis in HIV seronegative patients is variable. Fever is observed in approximately 50 per cent of cases. Severity, duration and presence of headache are quite vari-

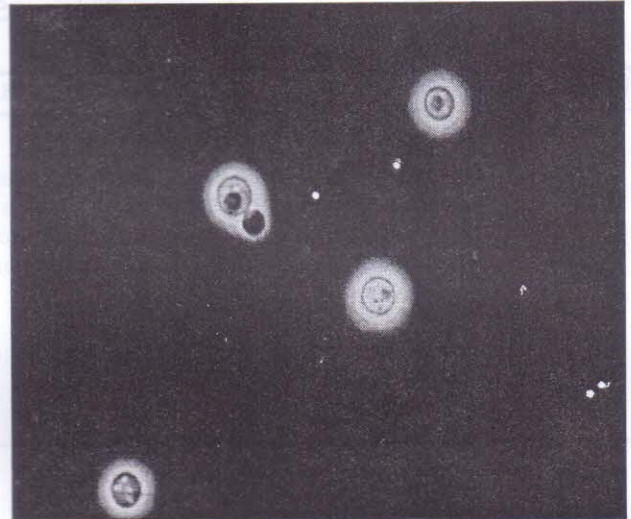


Fig. 1: India Ink stain showing budding *Cryptococcus neoformans* in CSF

able (Pappas *et al*, 2001). Many patients present with signs and symptoms of subacute meningitis or meningoencephalitis. Headache, lethargy, coma, personality changes, and memory loss typically develop over 2 to 4 weeks. Kiertiburanakul *et al*,(2006) showed that the most common associ-

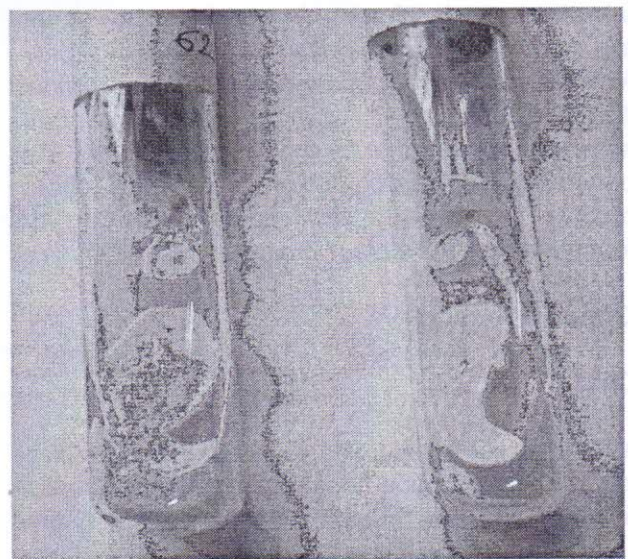


Fig. 2: Growth of *Cryptococcus* in SDA medium

ated conditions included immunosuppressive drug treatment (41%), presence of systemic lupus erythematosus (16%), malignancies (16%), and dia-



Fig. 3: Pemphigus foliaceus

betes mellitus (14%). Diagnosis of cryptococcal meningoencephalitis is difficult due to presence of nonspecific signs and symptoms. The disease should be suspected in patient presenting with fever, headache, neurological features, and sub-acute or chronic meningitis. Lumber puncture followed by cytology, biochemistry, culture, and cryptococcal antigen test are essential tools in diagnosis. Treatment of cryptococcal meningoencephalitis consists of antifungal therapy including induction, consolidation, and maintenance phases

using high dose Amphotericin B for more than 6 weeks followed by oral antifungal fluconazole in maintenance therapy (Perfect *et al*, 2010).

Cryptococcal meningoencephalitis should be a differential diagnosis in patients with immunosuppression due to any cause presenting with features suggestive of CNS infection. Certain cases are difficult to treat because they don't respond adequately to available antifungals particularly in regions where Flucytocine is not available.

ACKNOWLEDGEMENT

We are grateful to the Director, School of Tropical Medicine, Kolkata, for allowing us to work in this institution.

REFERENCES

- Dupont B. 1989. Cryptococcosis. *Bailliere's Clin Trop Med Commun Dis.* 4:113-124.
- Harrison's *Principles of Internal Medicine*, 17th edition, Vol-II, Cryptococcosis, 1251
- Kiertiburanakul, S., Wirojtananugoon, S. and Prachartam, R. 2006. Cryptococcosis in human immunodeficiency virus-negative patients. *Intl. Journal of Infect. Dis.* 10:72-78.
- Manson's *Tropical Diseases*, 22nd Edition, Cryptococcosis, pp 1186
- Pappas, P.G., Perfect, J.R., and Cloud, G.A. 2001. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis.* 33:690-9.
- Perfect, J.R., Dismukes, W.E.; and Dromer, F. 2010. Clinical practice guidelines for the management of cryptococcal disease: update by the infectious diseases society of America. *Clin Infect. Dis.* 50:291-322.