Case Report

CRYPTOCOCCAL MENINGITIS ASSOCIATED WITH TUBERCULOSIS IN HIV INFECTED PATIENTS

Urvinderpal Singh, Aditi, Pooja Aneja, B K Kapoor, S P Singh and Sukhpreet Singh Purewal

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Summary: Opportunistic infections are common complications of advanced immuno-deficiency in individuals with Human Immunodeficiency Virus (HIV) infection. Following involvement of the lung, the central nervous system (CNS) is the second most commonly affected organ. We report two cases of concurrent cryptococcal meningitis and tuberculosis (TB) in HIV infected persons. A high suspicion of multiple opportunistic infections should be kept in mind in HIV seropositive individuals. **[*Indian J Tuberc 2013; 60:* 180-183]**

Key words: Human Immunodeficiency Virus, Cryptococcal Meningitis, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is the most common opportunistic infection in patients with Human Immunodeficiency Virus (HIV). The estimated relative risk of HIV-infected individuals developing TB is 20.6 compared to HIV uninfected, in populations with a generalized HIV epidemic[1]. Cryptococcosis occurs worldwide and mostly affects the immuno-deficient individuals[2]. The condition has been reported more frequently since the emergence of AIDS. Cryptococcosis is the most common life threatening fungal infection in Aquired Immunodeficiency Syndrome(AIDS) with meningitis being the most common manifestation[3,4]. Because of increased immunosuppression due to HIV, we are coming across more cases harbouring multiple opportunistic infections such as tuberculosis and cryptococcosis[5]. Overlapping of the symptoms and delay in diagnosis is the main cause for increased mortality in such cases, thus a report of these cases.

CASE REPORT

Case 1: A-30-year-old male, known case of Pulmonary Tuberculosis was admitted with fever, severe headache, mental changes and increasing drowsiness of three weeks' duration. He was on continuation phase of anti-tubercular treatment. The patient was anaemic and emaciated, examination of the chest elicited bilateral vesicular breathing and coarse crepitations. CNS examination revealed the patient to be disoriented in time, place and person but responsive to verbal orders. Neck rigidity was appreciated. Laboratory evaluation revealed a hemoglobin of 10.5gm/dl, white blood cell (WBC) count of 12,500/cmm with 84% neutrophils and platelets 2,07,000/cmm. His urinalysis, liver, renal function tests and electrolytes were normal. Sputum was negative for AFB. As a standard protocol, he was tested for HIV and came out to be positive with a $CD4^+$ count of 97 cells/µl. ELISA test for HBsAg and Anti HCV was negative. His x-ray chest revealed bilateral heterogenous opacities (Fig. 1). Fundoscopy was normal. Contrast Enhanced Computerized Tomography (CECT) scan of the brain was normal. Cerebrospinal fluid (CSF) analysis revealed a cell count of 64 cells/cumm (100% lymphocytes), proteins 34mg/dl, sugar 31mg/dl and ADA was 5U/L. Gram and Ziehl-Neelsen (ZN) stain did not reveal any bacterial infection. CSF for Indian ink stain was positive for *Cryptococcus neoformans* (Fig. 2). Thus, patient was diagnosed as a case of cryptococcal meningitis. Alongwith anti-tubercular treatment, antifungal treatment was started with amphotericin B 50mg IV infusion/day at a dose of 1mg/kg/daily and fluconazole 400mg PO daily. Patient showed significant improvement after two

Department of Tuberculosis and Chest Diseases, Government Medical College, TB Hospital, Patiala.
Correspondence: Dr Urvinderpal Singh, 22, Baba Srichand Marg, Opposite: Government Press, Sirhind Road, Patiala – 147001 (Punjab); Email;singhurvinderpal@hotmail. com

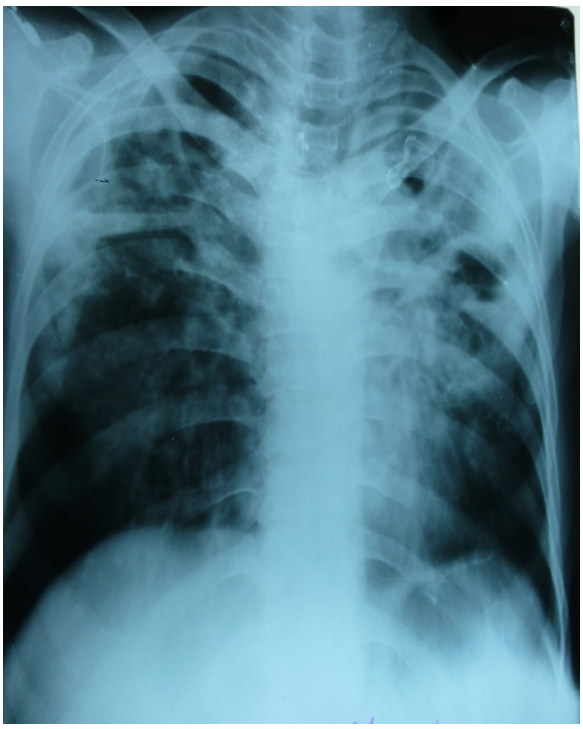

Fig 1: X-ray chest PA view showing bilateral heterogenous opacities.

weeks of antifungal therapy. Antiretroviral therapy(ART) was initiated after patient's condition stabilized. Patient was discharged in satisfactory condition after three weeks of stay in our hospital. Patient is on regular follow up and his general condition is stable.

Case 2: A-30-year-old married male was admitted in our hospital with severe headache, giddiness and painful sensitivity to light for the past three days, which was sudden in onset. Past history revealed that the patient was taking anti-tubercular treatment (ATT) since past two months for abdominal tuberculosis on the basis of contrast enhanced computed tomography(CECT) abdomen (Fig. 3) which showed lymphadenopathy, thickening of the ileocecal wall, ascitis and cytological evaluation of ascitic fluid. Patient was also showing signs of symptomatic improvement prior to this episode. On examination, the patient was anaemic and dehydrated. CNS examination showed the patient to be disorientated and neck rigidity was appreciated. Examination of the abdomen revealed diffuse tenderness. Other than a haemoglobin of 8.0gm/dl, the laboratory evaluation did not reveal any other abnormality. ELISA test for HIV 1 and 2 came out to

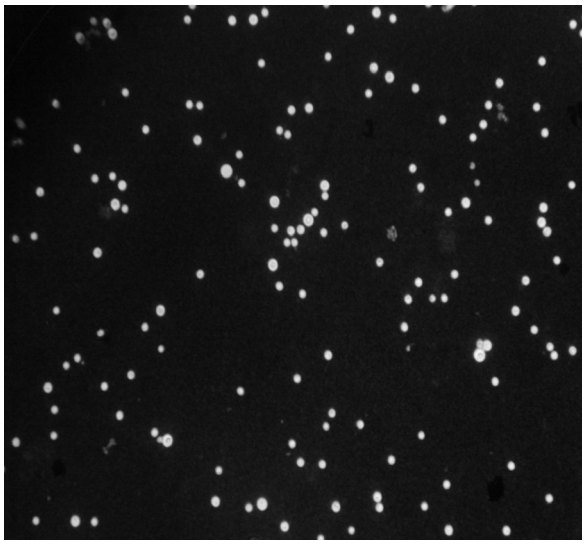

Fig 2: CSF sediment smear showing cryptococcal cells with capsule (Indian ink preparation at 40x magnification)

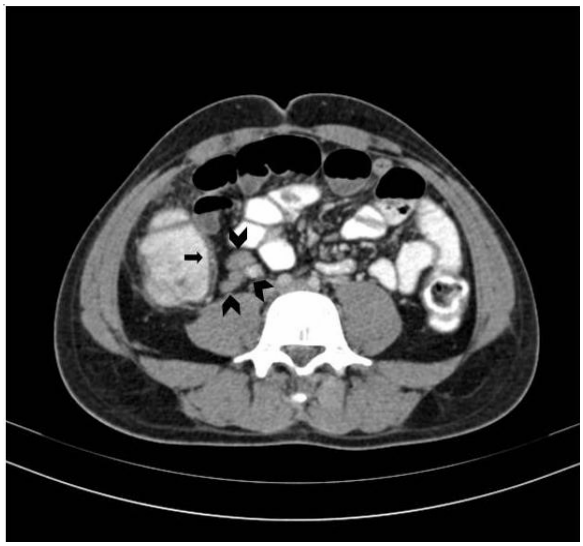

Fig 3: CECT abdomen showing ileocecal thickening (arrow) with lymphadenopathy (arrow heads)

be positive with a $CD4^+$ cell count of 7 cells/µl. However, ELISA test for HBsAg and Anti HCV was negative. Electrocardiography (ECG) of the patient did not reveal any abnormality other than sinus tachycardia. Fundoscopy also revealed no abnormality. Ultrasonography (USG) of the abdomen showed multiple lymphadenopathy with minimal ascites. Due to gradual deterioration in patient's condition, lumbar puncture was performed. CSF analysis revealed 52cells/cmm in CSF with lymphocytic pleocytosis (100% lymphocytes), raised protein (82 mg/dl) and low sugar levels (36 mg/dl). Gram and ZN staining did not reveal any bacterial infection. India ink smear of CSF sediment showed budding cryptococci with a capsule. The patient was diagnosed as a case of cryptococcal meningitis along with tuberculosis and HIV. The patient was advised antifungal treatment but patient left the hospital against medical advice and could not be followed up.

DISCUSSION

Both our cases were taking treatment for tuberculosis and their condition deteriorated during treatment and were admitted with suspicion of tubercular meningitis and subsequently diagnosed as being HIV positive and also suffering from cryptococcal meningitis. Another important fact is that in both the cases at the time of initiation of treatment for tuberculosis, screening for HIV was not done which is the protocol these days and if HIV infection had been detected earlier and ART initiated, meningitis due to cryptococcus neoformans may have been prevented.

HIV infection, which was first reported in India in the state of Tamil Nadu in 1986[6], has since spread to the entire country. Opportunistic infections are common complications of advanced immunodeficiency in individuals with HIV infection. Following involvement of the lung, the central nervous system is the second most commonly affected organ[7]. Tuberculosis is the most common opportunistic infection in HIV patients in India[8] and these individuals are at increased risk of all forms of extrapulmonary tuberculosis, including tuberculous meningitis[9]. Bhagwan *et al*[10] have highlighted the occurrence of tuberculous meningitis in patients already receiving antituberculous therapy.

Cryptococcosis, one of the AIDS defining infections, considered as "sleeping disease" became an "awakening giant" within a couple of years and has now been predicted as the "Mycosis of the future"[11]. Cryptococcal meningitis, a more serious form of meningitis, has been reported as the most common opportunistic infection of CNS of Indian patients with HIV infection[12]. Symptoms include headache, stiff neck, fever and painful sensitivity to light. Untreated cryptococcal meningitis is a disease associated with 100% mortality. Despite there being case reports of cryptococcal meningitis along with concurrent pulmonary tuberculosis[13], cryptococcal meningitis can be and is misdiagnosed as tuberculous meningitis, as reported in a few studies [14], especially in patients who are undergoing treatment for pulmonary tuberculosis. In both our cases also initially tubercular meningitis was suspected.

The $CD4^+$ T cell count is the best indicator of the immediate state of immunologic competence and also the strongest predictor of HIV-related complications in these patients. Cryptococcal infection was the major opportunistic infection and a major cause of death in HIV-infected patients with $CD4^+$ cell count <100 cells/µl in the pre-highly active antiretroviral therapy era[15]. The $CD4^+$ cell count in our cases was also very low 97cells/µl and 7 cells/µl respectively.

The diagnostic dilemma in both the cases was compounded as both the cases were taking treatment for tuberculosis. It has been stated that patients receiving antituberculous therapy were more likely to have tubercular meningitis[10], whereas Levy *et al* have suggested that in the presence of multiple opportunistic infections, the clinical findings of cryptococcal infection may get overlapped and confused with the findings of the other opportunistic infections[16] such as tuberculosis as in our cases.

By reporting these cases, we intend to create an awareness amongst clinicians that all cases diagnosed as suffering from tuberculosis must be screened for HIV and secondly, a high index of suspicion and laboratory work up are the need of the hour to diagnose and treat multiple opportunistic infections to improve survival in HIV patients.

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