Cryptococcal Meningitis in Acute Lymphoblastic Leukemia

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Abstract
The occurrence of cryptococcal meningitis in acute lymphoblastic leukemia (ALL), despite being immunosuppressed state is uncommon. We report a 28-year gentleman in the maintenance treatment phase of ALL developing cryptococcal meningitis. The diagnosis was made by positive India ink staining and detection of cryptola antigen by latex agglutination. The patient was successfully treated with amphotericin B. The rarity of this condition in ALL is briefly discussed.

INTRODUCTION
Cryptococcosis is a systemic mycosis most commonly involves the lungs and central nervous system and less frequently the skin, skeletal system and prostate. Cryptococci are usually found in bird excreta, soil, animals and can even colonize humans.1 Cryptococcal infection occurs most commonly in patients with impaired cell mediated immunity though cases have been described in patients with impaired antibody response and normal individuals.2 Patients with hematological malignancies are at a higher risk of developing cryptococcal infection though surprisingly such association has not been well described in acute lymphoblastic leukemia (ALL) patients.

CASE REPORT
A 28 years paramilitary personnel was diagnosed as a case of acute lymphoblastic leukemia and was put on treatment with modified BFM protocol.3 He was successfully induced with four drug regimen consisting of prednisolone, daunorubicin, vincristine and cyclophosphamide. Subsequently he received consolidation, prophylactic intracranial radiation and re-induction therapy. He did not have any episodes of febrile neutropenia during intensive phases of chemotherapy. The last cycle of chemotherapy including intrathecal methotrexate was administered 15 days prior to onset of symptoms. The fever was intermittent, moderate degree, accompanied by chills and rigors and was relieved by antipyretics. Headache was severe, constant, interfering with patient’s sleep, throbbing in nature and was associated with two episodes of vomiting. Patient denied history of blurring of vision, seizures or any focal neurological deficit.

Physical examination revealed a young man who was conscious and complaining of severe headache. His pulse rate was 90/min, blood pressure was 110/70 mm Hg, respiratory rate of 20/min, oral temperature of 38.3 °C. There was no lymphadenopathy or hepatosplenomegaly. There were no signs of meningeal irritation and fundus examination was normal. His investigations revealed hemoglobin of 9.9 gm/dl, total leukocyte count of 5.1 x 10^9 / L with 85% neutrophils,11% lymphocytes, 3% monocytes and no immature cells, platelets 175 x 10^9 / L, erythrocyte sedimentation rate of 65 mm in first hour, fasting plasma glucose of 4.7 mmol/L and a normal serum biochemistry. Chest roentgenogram was normal. Urine routine and cultures were normal. Blood cultures including cultures for fungus, serological assays for fungus, peripheral blood film examination for malarial parasites and Widal tests were non-contributory. Bone marrow was normocellular with less than 5% blasts. Plain and contrast-enhanced CT scan of head was normal. Cerebrospinal fluid (CSF) analysis showed a total leukocyte count of 360 cells/microL with 90% neutrophils, glucose of 3.05 mmol/L (corresponding blood sugar 7.77 mmol/ L), a total protein of 0.5 g/L. Gram stain and acid-fast bacilli stains of CSF did not reveal any organisms. The bacterial cultures were sterile. Flow cytometry did not reveal any malignant cells. India ink smear of CSF was positive for...
cryptococcus and cryptococcal capsular polysaccharide antigen was detectable by latex agglutination. The cryptola titers could not be done because of technical reasons. An enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) was negative. A diagnosis of cryptococcal meningitis was made and patient was administered amphotericin B (1 mg/ kg body weight/day). Fluconazole was not administered as the same was not available. Repeat CSF study done after a week of therapy showed 20 cells, predominantly lymphocytes, normal protein and glucose. India ink smear and latex agglutination tests were negative for cryptococcus. Patient was continued on amphotericin B for 4 weeks to a cumulative dose of 2 gms and discharged on oral fluconazole 200 mg daily as prophylaxis. Within 2 weeks of completion of treatment, patient presented with inguinal lymphadenopathy and bony pains. A repeat bone marrow examination showed 55% blasts; however CSF examination did not reveal any cryptococcus or malignant cells. Patient refused any further chemotherapy.

**DISCUSSION**

Cryptococcosis is an opportunistic fungal disease that occurs most frequently in immunocompromised hosts, especially persons with HIV infection or other diseases associated with T-cell dysfunction such as lymphoreticular malignancies, organ transplantation or corticosteroid therapy. The role of neutrophils in host defense against cryptococcus is not clear, as severe neutropenia is not a risk factor for development of cryptococcosis. However, in 20-30% of cases of cryptococcosis occurring in normal individuals, patient has no apparent underlying predisposing factors.

Cell-mediated immunity forms a major defense pathway against infection due to *Cryptococcus*. Immunological abnormalities have been described in apparently normal individuals with cryptococcal infection. Decrease in lymphocyte migration using cryptococcin and heat killed *Cryptococcus neoformans* as stimuli have been demonstrated. In addition, patients with past or ongoing cryptococcal infections have a decrease in delayed-type hypersensitivity to fungal skin test antigens but a normal lymphocyte transformation response to cryptococcin implying a defect in effector arm of lymphocyte directed immunity.

A review of literature for cryptococcal meningitis in lymphoreticular malignancies showed occurrence of cryptococcosis in patients with Hodgkin’s disease, non-Hodgkin’s lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia and in chronic myelogenous leukemia. However it has not been frequently reported in ALL. This observation suggests that patients of ALL, despite being immunocompromised, may be less likely to develop infections with *Cryptococcus*. The reason for this is not clear. The review of history in our patient revealed that patient military barrack was inhabited by pigeons. Thus environmental exposure to pigeon droppings and high dose of corticosteroids as given in maintenance chemotherapy for few days in the present case may be responsible for the disease. However, in most patients of cryptococcal meningitis the source of exposure is usually not very obvious. The other interesting aspect of this case is that patient relapsed within few days of completion of treatment for cryptococcal infection. As mentioned earlier, lymphocyte functions are abnormal in most patients with disseminated cryptococcosis. Although, initial bone marrow examination of the patient was normal at the time of diagnosis of cryptococcal infection, it seems likely that patient’s immunosuppression was because of impending relapse. The rarity of cryptococcal meningitis in ALL, unlike in other haematological malignancies, is thus intriguing.

**REFERENCES**