Concurrent Cryptococcal Meningitis and Falciparum Malaria in a Child with Nephrotic Syndrome

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Cryptococcosis is a fungal infection caused by the encapsulated yeast, Cryptococcus neoformans. Its incidence is increasing in patients, especially those with defects of cell-mediated immunity(1). The usual route of entry is probably via the lungs, where mostly the infection goes unnoticed and has a strong predilection for the central nervous system (CNS). The disease primarily presents as a subacute or chronic meningitis though other systems may also be involved. There are two varieties of cryptocooccus, i.e., C. neoformans var. neoformans (Serotype A, D, AD) and C. neoformans var. gatti, (Serotype B, C). Epidemiologically these two varieties have unique geographical distribution. The major environmental source of C. neoformans var. neoformans throughout the world is pigeon's excreta. Pigeon has a world wide distribution and occurs in high number and leads to large accumulations of infected dropping in sheltered habitats. Under favorable conditions the unique environmental niche may act as year round vector for the dispersal, where as the natural habitat of C. neoformans var. gatti is localized (2). Amphotericin B either alone or in combination with flucytosine has greatly improved the outcome of cryptococcal meningitis(3). We report a case of cryptococcal meningitis and concurrent falciparum malaria in a child with nephrotic syndrome.

Case Report

A fifteen-year-old male child was diagnosed as a case of nephrotic syndrome three years prior to the present admission to our hospital. He was being treated with prednisone. The exact doses of prednisone could not be obtained. One week before present admission, he had complained of moderate to high grade intermittent fever (104°F - 105°F) accompanied by chills and rigor. No associated history of vomiting, fits, visual disturbances or bowel bladder dysfunction was noted. During these febrile episodes, the patient's mental state was slightly impaired. He was hospitalized elsewhere and was provisionally diagnosed as a case of acute pyogenic meningitis. The child was treated with cefotaxime and amikacin. He was markedly irritable, complained of severe headache and was referred to our hospital. On the day of present admission, the child had fever, headache and vomiting. He was pale and febrile with a temperature of 101°F recorded in mouth. Physical examination
revealed facial puffiness with no lymphadenopathy. Chest was clear. Abdominal examination showed presence of ascites with no hepatosplenomegaly. Central nervous system (CNS) examination revealed evidence of meningeal irritation. There was no papilledema. His hemoglobin level was 9 g/dl, leukocyte count was 11,200/mm$^3$ and erythrocyte sedimentation rate (ESR) was 60 mm fall in 1st hour (Westergreen). Serum sodium, potassium, chloride and blood sugar levels were within normal limits. Human immune deficiency virus (HIV) serology was negative. Serum urea and creatinine levels were 62 mg/dl and 0.8 mg/dl, respectively. Twenty-four hours urinary protein was 0.8 g. Routine urine examination showed red blood cells (RBCs) 30-40 and pus cells 5-10/HPF, respectively. Liver function tests were within normal limits. Lumbar puncture was done which revealed sugar 15 mg/dl and protein 120 mg/dl. CSF cytology showed a total cell count of 475/cu mm with 157 lymphocytes, 75 polymorphs and 225 red blood cells.

Microbiological examination of CSF revealed Gram-variable spherical budding yeast cells. There was no mycelium or pseudomycelium. No bacteria was demonstrated. Encapsulated budding yeast cells with similar morphology were demonstrated in India ink preparation. Culture of the deposit on Sabouraud’s Dextrose Agar (SDA) grew Cryptococcus neoformans, which was confirmed by standard mycological techniques. Cryptococcus neoformans soluble polysaccharide antigen (CNSPA) was also detected in supernatant of CSF by latex agglutination test (cryptococcal antigen latex agglutination system CALAS, Meriden Diagnostic Inc., Cincinnati, Ohio). Identification was also based on positive urease test, and production of brown pigment in niger seed agar. Computed axial tomography (CT) showed no significant changes in CNS.

Urine, blood, sputum and other specimens were also investigated to look for probable dissemination by using both smear and culture techniques. None of the above investigations were positive. A peripheral blood smear (PBS) was also prepared just after the CSF was positive by both latex agglutination test and India ink to look for budding yeast. Giemsa stained PBS showed both asexual and sexual stages of Plasmodium falciparum. The quantitation of malaria parasites was done by WHO guidelines, with 500/μl of blood. The patient was treated with antimalarials and with antifungal drugs. Combination of sulphadoxin (20 mg/kg body weight) and Pyrimethamine (1 mg/kg body weight) was given in a single dose to treat falciparum malaria. The initial dose of amphotericin B was 0.3 mg/kg of body weight with gradual increase in dose up to 0.5 mg/kg of body weight combined with flucytosine (100 mg/kg body weight). Subsequent CSF examinations showed very slow clearance of cryptococcus. The response to therapy was judged by repeated antigen detection in the CSF. After culture became negative, the patient was switched on to fluconazole therapy (200 mg/day). Malarial parasite was not detected on repeated multiple PBS examination. The patient was discharged from the hospital with the maintenance therapy of fluconazole and treatment for nephrotic syndrome. No complications were noted during follow up and the patient had a good clinical recovery.

Discussion

Cryptococcal meningitis is of gradual onset, usually presenting with headache, loss of memory, poor concentration and in some signs of meningeal irritation and cranial nerve palsy. Symptoms of cryptococcal meningitis may be present for weeks.
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or months and may also be asymptomatic(7) and rarely be purulent as in bacterial meningitis(8,9) Cryptococcal infection is exogenous. Soil enriched with pigeon droppings has been incriminated as one of the major source of infection. The source and mode of infection in the present case was not clear. The patient was from a low socio-economic status and the probability of domestic surroundings rich in such soil could not be ruled out. During his six weeks of hospitalization, he was given 0.5 mg/kg body weight/day of prednisone.

The CSF profile in patients with cryptococcal meningitis shows raised protein in 90% of cases and sugar is reduced in 55%. The cell counts though variable is usually less than 300/mm³ and mainly lymphocyte(7). Erythrocyte sedimentation rate (ESR) is usually raised. Either plain or contrast CT scan is also indicated in patients with cryptococcal meningitis to detect associated hydrocephalus, cerebral edema and intracranial masses. Serotype status of clinical isolates also has epidemiological bearing as the apparent rarity of C neoformans var gatti infection in AIDS patients probably suggests the lower virulence(2) and to some extent predicts the mode of treatment.

Our patient was infected with serotype A of C neoformans var neoformans. Detection of antigen in the body fluid is both an adjunct to the diagnosis and an indicator of response to therapy. Although cryptococcal antigen in CSF may be positive for little longer duration even when the culture is negative, a gradual fall in titer is suggestive of good prognosis.

The recommended treatment for cryptococcal meningitis is a combination of amphotericin B (0.4-0.8 mg/kg/day)(8) with flucytosine (150 mg/kg/day) for six weeks(2). Patients who fail to respond to this combined regimen or those who relapse following appropriate therapy should be given either intrathecal or intraventricular amphotericin B(10,11). Our patient had received amphotericin B by intravenous route and flucytosine by oral route. Amphotericin B was given for six weeks and the total dose varied from 0.3 mg/kg/day to 0.7 mg/kg/day to obtain a proper fungistatic action.

Agents associated with nephrotic syndrome which could be of etiological significance are Plasmodium malariae, Hepatitis B, beta hemolytic streptococcus, Schistosoma, Filaria and Yersinia enterocolitica(12). In patients with Plasmodium falciparum infection, corticosteroids may increase and prolong the parasitemia(13), and might also be responsible for increased risk of other complications. The fact that Plasmodium falciparum has an immunosuppressive effect on its host(14), may predispose to the development of opportunistic infection. In the present patient, the questions which remain unanswered are - what could be the factors responsible for cryptococcal meningitis? Was it due to prolonged steroid (predinsone) treatment or due to immune suppressive effect of falciparum malaria? Cryptococcal meningitis is commonly seen in AIDS and other immunocompromised patients, however, coexistence of cryptococcosis has rarely been reported in patients with nephrotic syndrome and malaria.

REFERENCES


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Intestinal Lymphangiectasia

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Intestinal lymphangiectasia is a rare congenital disorder associated with protein losing enteropathy. It presents more often in the first two years of life with diarrhea and failure to thrive, and later with generalized edema due to hypoproteinemia(l). We report here a boy with intestinal lymphangiectasia.

Case Report

A 2 year and 11 month old boy presented in December 1994 with a history of recurrent episodes of generalized swelling of the body and loose stools for two years. He had been treated with plasma transfusion and antituberculous treatment in the past. He was the only child to his non-consanguineous parents. At birth, he was noticed to have facial asymmetry. He was breastfed for one year and at admission was on diet consisting of cow’s milk, rice, dhal, boiled

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