DISSEMINATED CRYPTOCOCCOSIS IN A PATIENT WITH NEPHROTIC SYNDROME

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Abstract

Disseminated cryptococcosis mainly occurs in patients with impaired cell mediated immunity. We present a case of disseminated cryptococcosis in a non-HIV patient with nephrotic syndrome who never received immunosuppression. Cultures of bone marrow aspirate, cerebrospinal fluid analysis and histology of skin lesions were all consistent with Cryptococcus neoformans infection. Treatment with amphotericin B followed by fluconazole was successful and in the course of two months when, the skin nodules disappeared.

Key words: Cryptococcus, nephrotic syndrome, immunocompromised host

With the increasing number of immunocompromised patients in the last decade, the systemic mycoses are increasing in importance as opportunistic infections. The etiologic microorganisms vary depending upon the type of immune dysfunction. Definitive diagnosis is often difficult to establish and usually requires invasive biopsy.

Cryptococcosis or Torulosis first described by Busse in 1894, is an uncommon systemic mycosis caused by the encapsulated yeast Cryptococcus neoformans. Approximately 85% of patients with cryptococcosis have impaired cell mediated immunity. Acquired immuno-deficiency syndrome (AIDS) associated cryptococcal infections now account for 80-90% of all patients with cryptococcosis.¹

Here we report a case of disseminated cryptococcosis in a non-HIV patient with nephrotic syndrome who was never treated with immunosuppressive drugs. We believe this case to be the first report of disseminated cryptococcosis occurring in a nephrotic syndrome patient without AIDS or medical immunosuppression.

Case Report

A 37-year-old farmer, who was diagnosed to have nephrotic syndrome, presented with one month history of low grade fever, lethargy, weight loss and increasing body swelling. Past medical history was significant for nephrotic syndrome, secondary to membranous glomerulonephritis two years back. He was treated with a diuretic and ACE inhibitor combination and never required steroids at any stage. He was however, lost to follow up for a year and was finally back with the above mentioned complaints.

On examination, he appeared ill, temperature was 100°F, blood pressure 160/90 mmHg, he was pale and had generalized oedema. General examination revealed multiple, variable sized, discrete, nontender subcutaneous nodules (Fig. 1) on the forearms, anterior abdominal wall and thighs; the overlying skin was normal.

Laboratory values revealed haemoglobin 68 g/L, total leucocyte count 21.8 × 10⁹/L, platelets 145 × 10⁹/L, ESR 90 mm/h, BUN 5.71 mmol/L, serum creatinine 99 µmol/L, total Bilirubin 4.44 µmol/L, direct bilirubin 0.34 µmol/L, alanine aminotransferase 24 units/L, aspartate aminotranferase 27 units/L, total proteins 64 g/L, albumin 13 g/L, globulins 51 g/L, albumin/globulin ratio 0.3. Blood and urine cultures, malarial parasite test and chest X-ray, were all unremarkable. 2D echocardiogram was negative for any vegetation. Ultrasound abdomen findings, which were later confirmed by CT scan, were suggestive of an old healed liver abscess in the right lobe of the liver. Without any other obvious clue to his fever,

Figure 1: Subcutaneous nodules on the right forearm. Also viable is the scar mark of excisional biopsy.
other than a possible liver abscess, he was started on intravenous metronidazole and ciprofloxacin. With fever persisting and blood cultures showing no growth, he underwent a bone marrow aspiration. Bone marrow cultures were reported positive for Cryptococcus neoformans. Excisional biopsy of the subcutaneous nodule was performed and after tissue homogenizer processing, inoculation onto Sabouraud glucose agar was done which revealed growth of Cryptococcus neoformans. Electron micrograph examination of the biopsy specimen was also consistent with the prominent capsule of Cryptococcus neoformans (Fig. 2).

Cerebro spinal fluid (csf) examination was done which revealed white cells 5 cells/µL, proteins 73 mg/dl and glucose 31 mg/dl, Cryptococcal antigen test by MYCO-Immune latex agglutination kit was positive but cryptococcal culture of the CSF was negative. Antibiotics were switched to intravenous amphotericin B at the dose of 1 mg/kg/day. Further workup included a negative HIV antibody testing by ELISA, decreased C4 levels and normal immunoglobulin levels. The patient became afebrile after 15 days of intravenous amphotericin B which was continued for 6 weeks (cumulative dose of 2.3 g) and later switched to peroral fluconazole 400 mg/day for 10 weeks. On follow up in clinic after two weeks, he was well; afebrile, had gained weight, oedema free, with serum creatinine was 91 µmol/L and the subcutaneous nodules were noted to regress in size.

Discussion

Cryptococosis neoformans has a worldwide distribution. Of the 19 species that comprise the genus Cryptococcus, human disease is associated only with Cryptococcus neoformans.2 Virulence of the organism plays a relatively small role in determining the outcome of an infection; the crucial factor is the immune status of the host, especially patients with defective cell mediated immunity such as patients with AIDS,1 corticosteroid use and organ transplant recipients. Patients with nephrotic syndrome are susceptible to a variety of infections due to numerous changes that occur in immune system even in the absence of immunosuppressive treatment. Several defects in cell mediated immune response have been described.3-5

The principal sites of cryptococcal infection are pulmonary, CNS and disseminated disease. Disseminated cryptococcosis is defined as recovery of Cryptococcus neoformans from blood, sterile body fluids or tissues other than pulmonary tissue. Cutaneous manifestations occur in 10-15% of cases and were the predominant feature of disseminated cryptococcosis in our patient.6,7

Clinical materials mounted in 10% potassium hydroxide or India ink reveal rounded yeast cells. Lysis centrifugation method of blood culture is the most sensitive and rapid. Body fluid aspirates or tissue sections can be inoculated onto Sabouraud dextrose agar or inhibitory mould agar. C. neoformans grows at 37°C, assimilates inositol, produces urease and melanin and does not produce mycelia on cornmeal agar. The yeast may be single or budding; rarely, pseudohyphae develop. Cell size varies widely between 3.5-8 mm in diameter.

Tissue specimens stained with haematoxyline and eosiin reveal large numbers of round yeast cells in a mucoid matrix, later a granulomatous reaction ensues. The capsules stain pink by mucicarmine technique. PAS and Gomori's methenamine silver stains can also be used to stain the organisms.8 Indirect evidence of infection by detection of cryptococcal antigens, particularly polysaccharide capsular antigen by latex agglutination test are particularly helpful and have high sensitivity and specificity.

In the absence of meningitis, localized lesions in skin, bone and other sites require systemic antifungal therapy. In cryptococcosis patients without HIV infection, the therapeutic goal is to achieve a permanent cure of the infection. This can be achieved by administering amphotericin B alone (for 6-10 weeks) or in combination with flucytosine (for 2 weeks), followed by fluconazole for a minimum of 10 weeks.8,9 In immunocompetent patients, drug therapy with amphotericin is effective in controlling infection in more than 70% of patients.10

With the increased number of immunocompromised patients, there has been a concomitant increase in patient morbidity and mortality due to fungi. A patient with nephrotic syndrome represents an immunocompromised host and hence is susceptible to a variety of infections. Clinicians should always consider cryptococcal infection in the differential diagnosis of an indolent febrile illness in an immunocompromised host.

Figure 2: Electron micrograph showing the capsule of Cryptococcus neoformans (x10,000).
References


Announcement

International Conference on “Leptospirosis: A diagnostic enigma” and the 6th Scientific Meeting of the Indian Leptospirosis Society

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