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POST TRANSPLANT CRYPTOCOCCAL MENINGOENCEPHALITIS IN A RENAL ALLOGRAFT RECIPIENT WITH TOLERANCE INDUCTION PROTOCOL- A CASE REPORT

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ABBREVIATIONS

CSF	Cerebrospinal fluid
ESRD	End stage renal disease
NIDDM	Non Insulin Dependent Diabetes Mellitus
CSA	Cyclosporine
HSCs	Hematopoietic stem cells

KEY WORDS

cryptococcal meningoencephalitis, renal transplantation.

ABSTRACT

Cryptococcal meningoencephalitis is the most common manifestation of cryptococcal infection in an immunocompromised host. It is difficult to diagnose cryptococcal meningitis in a posttransplant patient because of sub-acute and nonspecific presentation. We report an unusual early presentation of cryptococcal meningoencephalitis in renal allograft recipient who underwent pre-transplant tolerance induction protocol.

INTRODUCTION

Cryptococcal meningoencephalitis is the most lethal fungal infection occurring in an immuno-compromised host. Infection is caused by Cryptococcus neoformans, yeast like fungus, with world wide ubiquitous distribution. It is most commonly isolated from pigeon and chicken excreta. Infection is acquired by inhalation of airborne organism into the lungs.

CASE REPORT

A 43 years old male from Kenya, working as colonel in Navy, was admitted in our institute for renal transplantation. He had non-insulin dependent diabetes mellitus (NIDDM), hypertension and diabetic nephropathy leading to end stage renal disease (ESRD). He was on maintenance haemodialysis since 10 months, dialysis access was maintained through left subclavian perm catheter.

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He had one episode of acute idiopathic pancreatitis before 3 years which resolved with conservative treatment. After admission and evaluation for transplantation with brother as a donor, he willingly underwent tolerance induction protocol after giving informed written consent, as per the modified Helsinki guidelines.

The protocol included 2 donor leucocyte infusions followed by target specific (sub-diaphragmatic lymph nodes and part of pelvic bones), low dose (100 cGy x 4 on alternate days) irradiation. Conditioning included cyclophosphamide, 10 mg/ kg BW 2 couseatily days, polyclonal anti-lymphocyte globulin and cyclosporine (CsA), 3 mg/kg BW/ day, followed by infusion of donor hematopoietic stem cells (HSCs) obtained from cytokine mobilized marrow of donor, in to the thymus, iliac crest marrow, portal and peripheral circulation fortified by 2 doses of peripheral blood stem cells. He received 16.74 x 10^{8} cells/ kg BW unmodified HSCs, with mean CD 34+ count of 2.1 %. He was transplanted about 6 days after the last HSC infusion following negative lymphocytotoxicity cross-matching.

Posttransplant immunosuppression included CsA, 5 mg/kg BW/ day, from -2 days gradually tapered to 4mg /kg BW /day on 10^{th} post operative day; methylprednisolone, 500 mg, IV, on days -1,0,+1, followed by prednisolone, 0.5 mg/ kg BW/ day. Immediate post operative recovery was good and serum creatinine came down to 0.8 mg % on 10^{th} day.

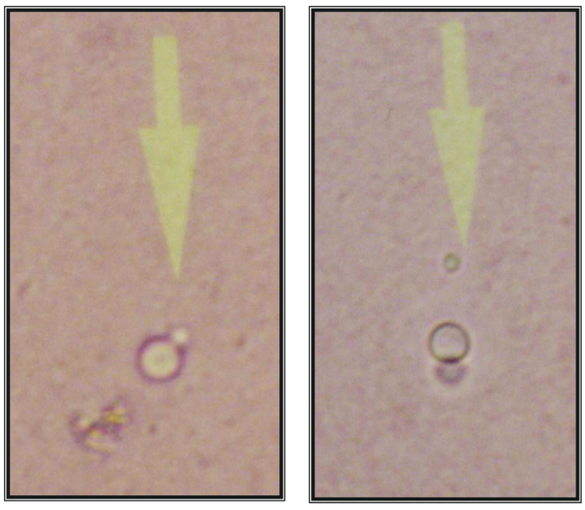

Figure (a) India Ink Preparation Demonstrating Capsule and Bud forms of Cryptococcus Neoformans.

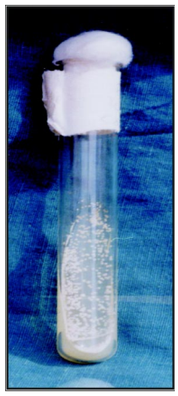

Figure (b) Sabouraud's Agar Showing Creamy-White Colonies of Cryptococcus Neoformans.

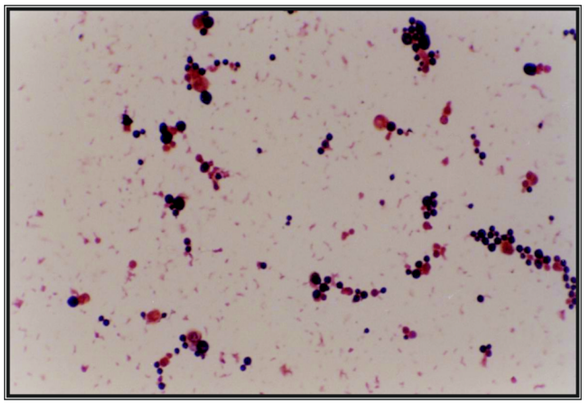

Figure (c) Gram Stain Demonstrating budding forms and Capsules of Cryptococcus Neoformans.

On 11^{th} post operative day patient developed headache which progressed to altered sensorium and decreased level of consciousness within 8 hours. There was no history of convulsion, fever, nausea or vomitting. On examination, all vital parameters were within normal limits. An oral candidiasis patch was present (since 2 days). His neurological examination did not reveal neurological deficit, other systemic examination was unremarkable.

Laboratory investigations showed hemoglobin: 9 gm %, total white cell count: 6600/c.mm, serum creatinine: 0.8 mg %, cerebro spinal fluid protein-120 mg /dl, sugar-20 mg/ dl, total cells-80 / cmm, with polymorphonuclear cells-60 %, lymphocytes-40 %. India ink preparation showed budding forms and capsules of Cryptococcus neoformans, cryptococcal antigen was also positive (figure a, b, c). Chest x-ray was normal.

Magnetic resonance imaging of brain revealed normal, mildly dilated ventricles.

Treatment: Patient was instituted on liposomal amphotericin B, 100 mg IV daily and immunosuppression was reduced. Patient was administered amphotericin for four weeks and CSF study was repeated, which showed absence of fungal buds on India ink preparation and all other parameters were within normal limits. He was subsequently switched from IV to oral dose, 200 mg/ day (Fluconazole).

At present, patient has serum creatinine of 1.2 mg % with prednisolone, 0.2 mg/kg BW/ day and CsA, 2.5 mg/kg BW/ day. He is also on prophylactic oral antifungal treatment.

DISCUSSION

Cryptococcosis is an infection caused by yeast like fungus Cryptococcus neoformans. This fungus grows well in smooth creamy-white colonies on Sabouraud's or other simple media at 20-37 ^{0}C. Identification of organism is based on gross and microscopic appearance, bio-chemical test and growth at 37 ^{0} C. The fungus has four capsular serotypes- A, B, C, and D (1). Patients with solid organ transplantation, glucocorticoid therapy or HIV infection are at increased risk of developing this infection. Incidence of serotype A infection is common; however serotype D occurs in up to 20 % of cases in Western Europe. Route of transmission is through lungs. Pulmonary infection has a tendency towards spontaneous resolution and is frequently asymptomatic. Silent hematogenous spread leads to clustering of cryptococci in perivascular areas of cortical gray matter, basal ganglia and to lesser extent in other areas of central nerrour system (CNS). Most of the patients have meningoencephalitis at the time of clinical diagnosis.

Manifestations of cryptococcal meningoencephalitis are non specific and often indolent in an immunosuppressed host. Usual manifestations in such host are only mild headache and altered level of consciousness. Classical signs of meningeal irritation are usually absent. Thus diagnosis requires a high index of suspicion. CSF findings in cryptococcal infection are lymphocytic pleocytosis, increased proteins and decreased sugar. India ink preparation shows encapsulated yeast in more than 50 % cases. Cryptococcal antigen shows positive report in 90% of patients. Diagnosis is conclusively established by CSF culture in doubtful cases. In most of the cases MRI remains normal, except for mild ventricular dilatation.

Our patient demonstrated similar findings. Treatment as per Infectious Diseases Society of America [2] guidelines for CNS infection, is amphotericin, 0.5-0.7 mg/ kg BW ± flucytosine orally, 100 mg/kg BW, divided in 4 doses every 6 hrly for two weeks or till CSF becomes sterile; followed by oral fluconazole, 400 mg /day for 6 months. Maintenance dose of 200 mg/ day is recommended in immunocompromised patient to avoid relapse. Itraconazole [3] can be used when fluconazole is not available, but is less effective than fluconazole.

Cryptococcal meningoencephalitis in renal transplant recipients occurs predictably between 1-12 months of post transplant period. Invasive fungal infections have been reported in 5-59 % of organ transplant recipients. The overall death rate in cryptococcal infection is around 20-100 %.

Out of 178 patients with posttransplant cryptococcal infection reported by Nina Singh et al, 98 % had meningitis and 2 % developed space occupying lesions in CNS. This study reported 42 % mortality. An interesting observation in this study was lower incidence of CNS involvement in cryptococcal infection with Tacrolimus due to its antifungal effect. KS Chugh et al, report an incidence of 6.13 % fungal infections in a cohort of 310 patients developing within 1 year posttransplant, with 42.1 % of these attributed to Cryptococcus species.

The incidence of posttransplant infections (including mycosis) is rare in our center due to the minimum immunosuppression required after tolerance induction protocol using high dose HSCT with minimum conditioning. We suspect that this African patient was harboring cryptococcal infection through his subclavian catheter used for maintenance dialysis. He had early and complete recovery with adequately functioning graft due to protective effect rendered with tolerance induction protocol.

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