Neurological worsening during treatment of an immunocompetent adult with *Cryptococcus neoformans* meningitis

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\textbf{A B S T R A C T}

Cryptococcal meningitis is being increasingly described in immunocompetent adults. We describe here a young immunocompetent adult of Indian origin from Ghana, West Africa with cryptococcal meningitis who had several ups and downs during his treatment. First he developed neurologic worsening due to premature transition from intensive to consolidation phase therapy. Subsequently he deteriorated due to “immune reconstitution inflammatory syndrome (IRIS)” like phenomenon that necessitated the prolonged use of steroids. Additionally he suffered serious adverse effects due to antifungal drugs including liposomal amphotericin B and fluconysone. He recovered after 16 months of treatment. The case highlights the possible difficulties in management of cryptococcal meningitis in immunocompetent host including ‘immune reconstitution like syndrome’. There is need for new trial data and guidelines about treatment of cryptococcosis in the non HIV host.

1. Introduction

Cryptococcal meningitis is primarily a disease of the immunocompromised host chiefly the HIV infected. A recent review estimated that there are around 2,00,000 incident cases of cryptococcal meningitis in HIV infected patients globally every year with 79% in Sub-Saharan Africa. The annual global deaths from cryptococcal meningitis were estimated at 181,100 of which 75% deaths were in Sub-Saharan Africa \cite{1}. In the developed world while the main risk factors for cryptococcal meningitis include HIV and other immunocompromised states, cases in apparently immunocompetent adults are increasingly being recognized \cite{2}. Many of these are due to \textit{C. gatti} and have treatment outcomes that are poorer than the HIV infected \cite{2} Also unlike HIV infected patients where new regimes are constantly being evaluated, there is paucity of data about treatment in the non HIV host and practice guidelines are almost two decades old \cite{3}. We describe here an immunocompetent adult of Indian origin living in West Africa with *Cryptococcus neoformans* meningitis who experienced significant morbidity due to disease relapse, paradoxical upgrading reaction as well as side effects of antifungal drugs.

2. Case

A 34 year man of Indian origin living in Ghana, West Africa presented with a three week history of low grade fever, headache and recurrent episodes of transient self remitting hemiparesis (on either side). He had recent-onset mild diabetes that was well controlled on dietary therapy. MRI brain showed meningeal enhancement and a CSF exam revealed cryptococcal meningitis. The patient decided to travel to India for further treatment. On arrival at our centre, he was conscious, oriented, febrile, had significant headaches and looked ill (Day 0). There was papilloedema, mild left ataxic-hemiparesis and dysarthria. He reported recent and close exposure to pigeons. A repeat MRI brain (Day 0) on contrast sequences, showed diffuse meningeal enhancement with spinal arachnoiditis. There were tiny acute and subacute infarcts in bifrontal region (Fig. 1a–c). CSF day 0 showed features of inflammation with opening pressure of 20 cm of H\(_2\)O and CSF cryptococcal antigen was positive and cultures were sent (Table 1). Around 30 ml CSF was drained. CD4 counts were normal and tests for HIV and VDRL were negative. Induction therapy with intravenous amphotericin B deoxycholate (1mg/kg/day) and fluconysone (100mg/kg/day) was commenced. However, on the second day of treatment (Day 1), amphotericin B deoxycholate was substituted with liposomal amphotericin B (3 mg/kg/day) due to allergic reaction to the former. MRI (Day 10) showed resolution of meningeal enhancement seen on the earlier scan. CSF on Day 9 also showed improvement in opening pressure, pleocytosis and cryptococcal antigen titres (Table 1). Over the next two weeks, the fever and papilloedema resolved and hemiparesis
recovered. Treatment was switched to from induction phase (ampotericin B plus flucytosine) to consolidation phase of therapy (oral fluconazole, 800 mg/day) as at the end of two weeks as the patient had shown marked clinico-laboratory improvement, and was suffering from refractory hypokalemia. CSF cultures grew *C. neoformans var grubii* on Day 18. On day 28, two weeks after initiating oral fluconazole, the patient developed headaches, vomiting, papilloedema and horizontal diplopia. Brain MRI showed re-emergence of meningeal enhancement on contrast sequence (Fig. 2a–c). CSF on Day 28 revealed sugar levels of 56 against a random blood sugar of 201 as against 96/156 earlier and cell count of 90 as against 20 earlier and protein of 45 mg% as against 27 mg% earlier (Table 1). However CSF cultures sent on day 9 CSF examination were negative. The temporal profile of this event suggested that this was a relapse possibly due to early transition to the consolidation phase of treatment. Therefore induction therapy with liposomal amphotericin B and flucytosine was reinitiated and fluconazole discontinued. Over the next few days the neurological signs reversed. However, by Day 42, two weeks after reinitiating fluconazole, the drug was discontinued as the patient developed severe pseudo-membranous colitis and axonal sensorimotor neuropathy. The cultures sent on day 9 and day 28 CSF remained negative.

On Day 56 while the patient was still on induction therapy, the patient developed headaches, vomiting and imbalance. A repeat brain MRI again showed worsening meningeal enhancement (Fig. 3a–c). CSF examination at this time was not suggestive of ongoing infection (increase in CSF sugar to 76/187 as against 56/201 earlier; decrease in cell count to 30 as against 96 earlier and cryptococcal antigen to 1:8 from 1:16 earlier). Therefore, this second episode of neurological deterioration (while on induction therapy) was considered to be a paradoxical immune upgrading reaction. Steroids (dexamethasone 12 mg/day) were initiated and liposomal amphotericin B continued for a total of six weeks (Day 28–Day 70). Consolidation therapy with fluconazole at 800 mg per day was started (patient weighed 90 kg). There was rapid clinical improvement and steroids were tapered gradually and eventually stopped in 1 month (Day 82). By day 86 however the patient experienced headache therefore steroids at prednisolone 20mg/day) were given for another two weeks (till day 100) and slowly tapered over the next three months (day 190) with sustained clinical improvement. Fluconazole was given as 800mg per day from day 70- day 130 (2 months) then 400 mg per day from Day 130- Day 480 (12 months). On follow up over the next 24 months the patient has remained well and resumed work. Serial brain MRI over this period continue to be normal (Fig. 4a–c). The flucytosine-induced neuropathy has shown significant clinical and electrophysiological improvement.

### Table 1

| Date     | Opening pressure (cm of CSF) | Cells/ml (% of lymphocytes) | Sugar mg/dl (parallel blood sugar) | Protein mg/dl | Cryptococcal antigen titre | Culture |
|----------|------------------------------|----------------------------|-----------------------------------|---------------|----------------------------|---------|
| Day 0    | 20                           | 70 (87%)                   | 125 (248)                         | 36            | 1:1024                     | Positive|
| Day 9    | 13                           | 20 (78%)                   | 96 (156)                          | 27            | 1:64                       | Negative|
| Day 28*  | 17                           | 96 (78%)                   | 56 (201)                          | 45            | 1:16                       | Negative|
| Day 56** | 15                           | 30 (84%)                   | 76 (187)                          | 62            | 1:8                        | Negative|
| Day 70   | 16                           | 1                         | 123 (130)                         | 18            | 1:16                       | Negative|

* time of first neurological deterioration due to disease relapse.  
** time of second neurological deterioration due to paradoxical immune reaction.

### 3. Discussion

We report the successful management of neurological worsening from disease relapse after an early switch from induction to consolidation phase of treatment as well as treatment induced paradoxical-
immune reaction in a young immunocompetent adult with *Cryptococcus neoformans* meningitis. Our report also highlights the challenges and adverse effects seen while using antifungals for prolonged periods.

Cryptococcus meningitis should be suspected and evaluated for in both immunocompetent and immunocompromised patients. The disease is complex to treat more so in the immunocompetent with some series reporting mortality rates of 44% in excess to those seen in HIV infected hosts [2]. This has been attributed to delayed diagnosis, suboptimal antifungal therapy and possibly host immune responses [2]. Standard recommendations for treatment of cryptococcal meningitis in the non immunocompromised therefore include a longer intensive phase of therapy of 4–6 weeks with amphotericin B and flucytosine in contrast to HIV infected patients where 2 weeks of induction therapy is

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**Fig. 2.** Contrast axial T1 (Fig. 2a) showed worsening of cranial meningitis with new vasculitic infarcts in both cerebellar hemispheres on diffusion images (Fig. 2b and c).

**Fig. 3.** Contrast axial T1 (Fig. 3a and b) and contrast sagittal T1 spine images (3c) show further worsening of cranial meningitis, especially in posterior fossa with nodular pial enhancement in cerebellar fissures. Spinal cord and cauda equina.

**Fig. 4.** Contrast axial T1 images (Fig. 4a and b) and contrast T1 sagittal of spine (Fig. 4c) show near resolution of meningitis with mild residual enhancement in the cerebellum.
considered sufficient [3]. However, the same guidelines do mention shortening the induction therapy to two weeks in those with low risk of therapeutic failure defined as early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state, and an excellent clinical response to initial 2-week antifungal combination course such as seen in our case. However, the occurrence of relapse in our patient despite using the recommended high doses of fluconazole (800 mg/day) suggests that prolonged induction therapy is probably a safer option especially given the fact that he had stroke like episodes at the onset of the disease suggesting advanced disease at the time of presentation.

The second deterioration while on therapy with liposomal amphotericin B and fluconazole and response to corticosteroids are sufficiently diagnostic of a paradoxical reaction. Paradoxical reactions or immune reconstitution inflammatory syndrome (IRIS) in cryptococcal meningitis in HIV have been described in almost 30% of patients [4]. Paradoxical upgrading reactions (PUR) in the non immunocompromised host with cryptococcal meningitis have been previously reported with C. gattii infection [5–10]. Some of these patients have been treated with corticosteroids with good outcome. It is hypothesized that treatment with antifungal therapy leads to decline in the levels of cryptococcal polysaccharide associated with reversal of the immunosuppressive effects of the polysaccharide capsule with a shift to TH1 response and inflammation. Treatment with L AmB which has an immunomodulating effect may be better to prevent IRIS in non HIV patients than AmB D which has a greater inflammatory effect and can be used to advantage in the highly immunocompromised HIV patients. PUR has been infrequently described with C. neoformans. In a recent paper, Panackal et al described paradoxical reactions in two non HIV infected individuals, one with Cryptococcus neoformans infection [11]. Steroids were used in both instances with favourable responses. They proceeded to describe a cohort of 17 patients with no known immunocompromise with severe cryptococcal CNS disease (10 cryptococcus neoformans, 5 gatti and 2 untyped). Fourteen of these 17 patients needed adjunctive prednisone to control cerebral edema. Detailed immunologic studies revealed that while these patients had effective microbiological control, they displayed strong intrathecal expansion and activation of HLA-DR + CD4+ and CD8+ cells and NK cells. These cells expressed high levels of IFN-γ as well as a lack of elevated CSF levels of typical T-cell specific Th2 cytokines – IL-4 and IL-13. This inflammatory response was accompanied by elevated levels of CSFNFL (neurofilament), a marker of axonal damage, consistent with ongoing neurological damage.

The index case and review of literature thus suggests that a subset of immunocompetent patients with cryptococcal meningitis are likely to experience clinical deterioration after starting antifungal therapy and will benefit from early institution of corticosteroids. This worsening should be carefully differentiated from therapeutic failure or relapse on shifting to consolidation/maintenance therapy. It should also be remembered that use of steroids for IRIS/PUR may predispose to a future relapse of the disease [12]. Whether routine use of corticosteroids is mandated in all immunocompetent patients with cryptococcal meningitis akin to tuberculous meningitis is a question that remains to be answered [13]. In this context, it is important to note that adjunctive use of dexamethasone in patients with HIV associated cryptococcal meningitis did not reduce mortality but was associated with increased disability, adverse effects and delayed microbiologic clearance [14].

Our patient required three months of hospitalization and 15 months of antifungal use. Antifungals are associated with frequent and at times dose-limiting adverse effects. Our patient developed adverse reactions to both amphotericin B (acute hypersensitivity reaction and refractory hypokalemia) and fluconazole (pseudomembranous colitis and partially reversible sensori-motor neuropathy).

To sum it all, treatment of cryptococcal meningitis is challenging and extremely resource intensive. There is need for new trial data and guidelines for treatment of this complex disease in the non HIV infected host.

Declaration of competing interest
None.

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