

IRIS due to cryptococcal meningitis ten years after the initial episode in a HIV positive patient with a high CD4 count and suppressed viral load – A case report

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Abstract

Cryptococcus neoformans is a fungus which causes opportunistic infection in patients with Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS) with meningitis being the commonest presentation in HIV affected individuals. A CD4 T cell count <200 has been shown to be the strongest risk factor for meningitis, and the mean CD4 count in HIV-related cryptococcal disease is <100 with a range of 75 to 125. Affected individuals are put on secondary fluconazole prophylaxis, in the absence of which 50 to 60% develop relapse. As virtually all patients receive anti-retroviral therapy (ART), relapse and immune reconstitution inflammatory syndrome (IRIS) following ART are well described in the initial months after starting ART. We report a case of late onset IRIS in an immune reconstituted patient with a high CD4 count and suppressed viral load.

Keywords

cryptococcal meningitis relapse, CD4 counts, cryptococcus in HIV

Case Presentation

A 44 year old male was diagnosed with HIV/AIDS (CDC C, WHO 4) in 2004 after presenting with cryptococcal meningitis. His baseline CD 4 count was 16 cells/cmm and HIV viral load was 47,259 copies / ml. His serum and cerebrospinal fluid (CSF) cryptococcal antigen (CRAG) were positive and CSF India ink preparation was positive for cryptococcus. He also had hepatitis B co-infection with a hepatitis B viral load of 750000. He was treated with intravenous amphotericin B deoxycholate and high dose fluconazole. He was then started on ART (zidovudine, lamivudine and efavirenz), improved clinically and was maintained on chronic suppressive therapy with fluconazole till 2006. His serial CD4 counts and HIV viral loads are given in Table 1.

His ART was switched to Tenofovir, Emtricitabine, Efavirenz (TDF/FTC/EFV) in 2009 to treat concomitant hepatitis B. He was admitted in March 2014 with difficulty in walking, increased forgetfulness and severe headache. On examination he had mild neck stiffness. Investigations showed normal haemogram, renal and Liver Function Tests. At this time, CD4 count was 485 cells/cmm and HIV viral load was undetectable [<Less than Detectable Limit (LDL)] (Table 1). MRI brain showed leptomeningeal contrast enhancement suggestive of meningitis with non uniform hydrocephalus with

multiple segmentation (Figure 1, 2).

CSF analysis showed a WBC count of 280 (Neutrophils 1%, Lymphocytes 98%), protein level was 580mg/dl and glucose was 29mg/dl. Serum and CSF cryptococcal antigen (CRAG) were positive. CSF India ink preparation for cryptococci was negative. Gene Xpert for MTB done on CSF was negative. CSF culture for bacteria, fungi and mycobacteria were negative. CSF HIV viral load was 126 copies / ml. He was treated with intravenous amphotericin B and flucytosine, and then switched to fluconazole prophylaxis. He improved clinically and was doing well at 6 month follow up.

Discussion

AIDS related cryptococcal meningitis has been of utmost concern as it is associated with high mortality if not treated with appropriately. Though *Cryptococcus* affects skin and lungs, meningitis is very common in the HIV affected individuals. It chiefly chooses to affect the severely immune compromised especially in those whose CD4 count is less 100 [1]. It is the second leading cause of morbidity and mortality in AIDS patients [2,3]. Those who are already known cases of HIV, developing cryptococcal meningitis if not under treatment are associated with higher mortality. The other problem encountered in HIV is immune reconstitution inflammatory syndrome which occurs in those who are initiated on ART [4]. "Immune reconstitution inflammatory syndrome" (IRIS) is condition where paradoxical worsening of preexisting infectious processes or unmasking of hidden infections occurs after the initiation of highly active antiretroviral therapy (HAART) in HIV-infected individuals [5]. As the immune function improves after the initiation of HAART, systemic or local inflammatory reactions may occur at the site or sites of the preexisting infection. IRIS is usually a self-limiting condition; but can be life threatening if central nervous system is involved.

Two important complications of cryptococcal meningitis are relapse and IRIS. Relapse has been defined as the reappearance of clinical symptoms (symptomatic relapse) and the recovery of viable cryptococci in previously sterile CSF (microbiological relapse) [6,7]. Our patient did not fit criteria for microbiologic relapse. Reasons for relapse include absence of secondary prophylaxis after an episode of meningitis [8], poor compliance with fluconazole therapy [9] and fluconazole resistance [10,11].

An important cause of symptomatic meningitis is IRIS following immune reconstitution with ART. Fungal cultures are typically negative, and the diagnosis is made by cryptococcal antigen testing and the temporal occurrence after ART [4,7]. Typical risk factors include low CD4 count (usually <50) or early initiation of ART. As we could not see or grow cryptococci from CSF, our patient appeared to have IRIS rather than relapse.

Our patient was unusual in that he became symptomatic 10 years after initiation of ART and 8 years after secondary prophylaxis with fluconazole was discontinued and had a CD4 count of 485 when IRIS occurred. This is distinctly different from the literature which describes IRIS in the first few months after ART initiation and at low CD4 counts, typically <100 [4,7].

Table

Table 1: CD4 count and HIV viral load over 10 year period

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cd4 (cells/cmm)	16	85	125	215	175	183	277	300	254	485
HIV Viral load (copies/ml)	47259	<LDL								

Figures

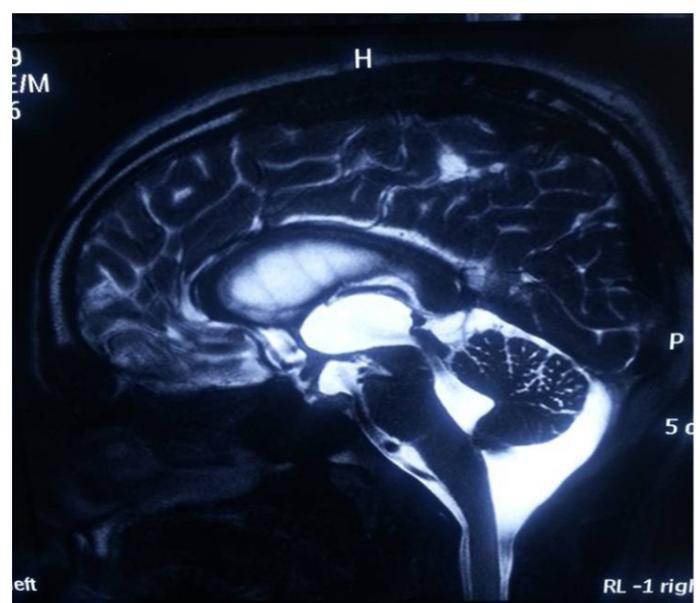
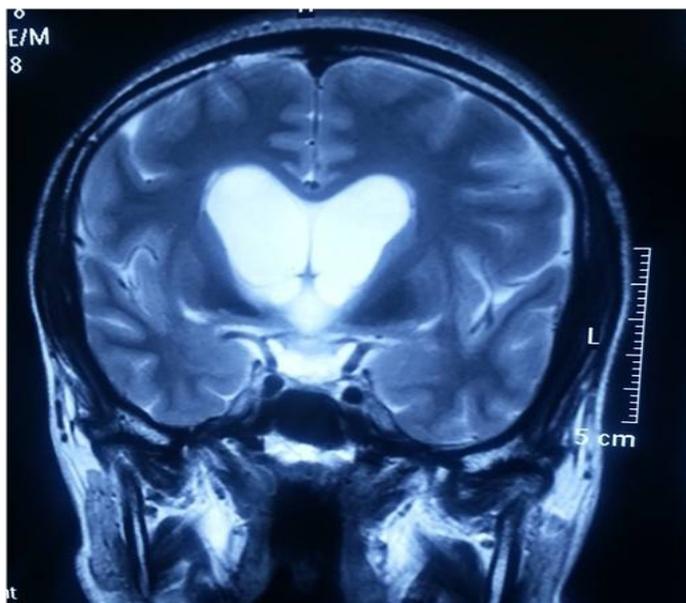


Figure 1: MRI brain showed leptomenigeal contrast enhancement suggestive of meningitis with non uniform hydrocephalus with multiple segmentation
Figure 2: MRI brain showing non uniform hydrocephalus with multiple segmentation

Conclusion

Our case illustrates the importance of remaining vigilant for IRIS in patients with a history of cryptococcal meningitis, even in patients with high CD4 counts and suppressed viral loads many years after the initial episode of meningitis.

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