Medical journal armed forces india manuscript health and social care essay

Medical Journal Armed Forces India Manuscript DraftManuscript Number: MJAFI-D-13-00091Article Type: Case ReportKeywords: IRIS; Cryptococcus; HAARTAbstract: The immune system recovery in a HIV positive patient who is being treated with HAART leads to a paradoxical increase in immune responses. This is what is known as Immune reconstitution inflammatory syndrome (IRIS). We describe a case of Cryptococcal IRIS in a 39 yr old male who presented with history of short febrile illness, altered sensorium and global headache. Clinically he had fever, altered sensorium, terminal neck stiffness with no localizing signs. Routine hematological and biochemical examination were essentially within normal limits. Urgent CECT brain revealed a normal study. He was found to be reactor for HIV 1. His CD4 count was 12 cells/mm3 and the HIV-1 viral load 428, 714RNA copies/ml. CSF analysis showed a mild increase in cell count (lymphocytes) and protein. CSF culture was sterile. Patient was put on HAART and managed with injectable (Ceftriaxone and Acyclovir) and he showed gradual recovery. On the 6th day of treatment he again had severe headache, fever, vomiting and started behaving abnormally. A repeat CSF analysis showed a further increased cell count and protein and a low sugar level. Culture showed Cryptococcus neoformans growth (susceptible to Amphotericin B). However despite intensive drug regimen, his condition rapidly deteriorated and he succumbed to his illness on 14th day of his admission. IRIS with cryptococcal meningitis is rare and its diagnosis is challenging. Hence confirmation of the disease relies heavily upon case definitions incorporating clinical and laboratory data. It should be suspected in patients who show clinical, radiological or pathological deterioration following initiation of HAARTIntroductionThe HAART for HIV infection has led to significant decline in AIDS-associated

morbidity and mortality. These benefits are, in part, a result of partial recovery of the immune system, manifested by increase in CD4+ T-lymphocyte counts and decrease in plasma HIV-1 viral load. However the immune system recovery also leads to a paradoxical inflammatory reaction against a foreign antigen (alive or dead) in patients who have started antiretroviral therapy and who have undergone a reconstitution of their immune responses. This is what is known as Immune restoration disease (IRD) or Immune reconstitution inflammatory syndrome (IRIS). This syndrome has been described in association with various opportunistic pathogens like Mycobacterium avium complex, Mycobacterium tuberculosis, Cryptococcus neoformans, Cytomegalovirus and Hepatitis viruses (1). The incidence of Cryptococcal IRIS varies from 8%–50% of AIDS patients who were started on HAART (2)Case reportA 39 yr old married male presented in the emergency OPD of a tertiary care center with history of short febrile illness, altered sensorium and global headache. Clinically he had fever, altered sensorium, terminal neck stiffness with no localizing signs. Routine hematological and biochemical examination were essentially within normal limits. Urgent CECT brain revealed a normal study. He was found to be reactor for HIV1. His CD4 count was 12 cells/mm3 and the HIV-1 viral load 428, 714 RNA copies/ml. CSF analysis showed a mild increase in cell count (lymphocytes) and protein. CSF culture was sterile. Patient was put on HAART and managed with injectables (Ceftriaxone and Acyclovir) and he showed gradual recovery. On the 6th day of treatment he again had severe headache, fever, vomiting and started behaving abnormally. A repeat CSF analysis showed a further increase in cell count and protein as well as a low sugar level. Culture showed Cryptococcus neoformans growth (susceptible to Amphotericin B).

However despite intensive drug regimen, his condition rapidly deteriorated and he succumbed to his illness on 14th day of his admission.

DiscussionCryptococcal immune reconstitution inflammatory syndrome (C-IRIS) may present as a clinical deterioration or new presentation of cryptococcal disease following initiation of antiretroviral therapy (ART) and is believed to be caused by recovery of cryptococcusspecific immune responses. A consensus case definition pertaining to this disease entity, has arrived upon two distinct terminologies-a) Paradoxical cryptococcal IRIS in which patients have known cryptococcal disease prior to ART and who subsequently deteriorate while on ART (3) b) ART-associated cryptococcosis where an incident case of cryptococcosis develops during ART (4). A provisional entity of " unmasking" C-IRIS is also included under this heading. Infection with Cryptococcus neoformans may remain latent for years and is not uncommon to see them re-emerge in severe immunodeficiency, after initiation of ART therapy. Clinically both these forms present in any of the following forms (a) meningitis (2/3 rd cases) (b) space-occupying CNS lesions (c) Necrotic lymphadenopathy (d) Pneumonitis(e) Suppurative soft tissue lesions. Though largely similar, ART associated CM often presents with rapid onset of severe illness over a few days as compared to a sub-acute course typically seen with cryptococcal meningitis (CM) in patients not receiving ART(3)The timing of cryptococcal IRIS after HAART initiation appears to be variable, ranging from less than 1 week to several months (5). Furthermore, most patients who develop IRIS have had high viral loads and very low CD4+ T-lymphocyte (CD4+) counts, as was also seen in our case. Confirmation of a virologic response (reduction in VL of <1 log10) to ART is recommended, but not essential, for the diagnosis of C-IRIS. In our case, due to the fatal course

of events, the repeat viral load could not be done. The underlying pathogenesis of this disease is a marked type-1 CD4 T-helper (Th1) response present in serum and CSF. Persons at risk for C-IRIS have scarce inflammation and ineffective antigen clearance prior to ART, followed by antigen presentation on ART and probably a deregulated antigen-specific and generalized pro-inflammatory response (6). A central pathogenic role for an alteration in Th1/Th2 balance has also been proposed. Few studies also suggest that elevated C-reactive protein (CRP) and IL-6, 7, 13 concentrations precede the development of C-IRIS, compared with ART-treated individuals with cryptococcosis who do not experience IRIS (7). CSF examination remains an important investigation in the work up of these cases. A relatively higher CSF opening pressure and cell count favours a C-IRIS over non IRISCM. An increased pro inflammatory cytokine profiles (e. g. IFN-γ, TNF-α, IL-12, IL-17) at time of clinical deterioration, may distinguish C-IRIS from CM-relapse. The role of cryptococcal antigenemia, reflected in previous studies, in the diagnosis of C-IRIS is controversial (8). Neither a positive nor negative serum/ CSF CrAg prior to the start of ART is an exclusion criterion for ART-associated cryptococcosis. Hence the non-conductance of this test in our case. However, we reckon that pre-ART screening for cryptococcal antigenemia may be a useful strategy for identifying and treating subclinical infection and reducing the incidence of ART-associated cryptococcosis in high prevalence regions. The CSF culture not only confirms the diagnosis but also gives us a valuable guidance in selecting the antifungal of choice. The automated microbiological organism detection and ABST machine (VITEK 2) at our laboratory confirmed our clinical suspicion of CM. ConclusionIRIS with cryptococcal meningitis is rare and its diagnosis is challenging. There are

many overlapping syndromes and many newer concepts regarding the pathogenesis, diagnosis and treatment aspects are coming up. The confirmation of the disease relies heavily upon case definitions incorporating clinical and laboratory data. It is pertinent for us to be aware of this entity and have high index of suspicion in patients who show clinical, radiological or pathological deterioration following initiation of HAART. Conflicts of interests-none