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Tuberculosis and cytomegalovirus retinitis : IRIS in a HIV-infected individual

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Abstract

Immune reconstitution inflammatory syndrome (IRIS) is not a rare incidence after the initiation of highly active anti-retroviral therapy (HAART). We reported a case of a 36-year-old individual who had Human Immunodeficiency Virus (HIV) and deteriorated two weeks after initiation of HAART. He was diagnosed as IRIS with tuberculosis-lymphadenitis and Cytomegalovirus infection of left eye. He had a prolonged stay in hospital for eleven weeks.

Keywords

immune reconstitution inflammatory Syndrome; human immunodefiency virus; highly active anti-retroviral therapy

Introduction

The number of individuals with Human Immunodeficiency Virus (HIV) increases every year in Sarawak, Malaysia. There is a worrying trend that most of the cases are transmitted through men having sex with men (MSM) activity. Management of HIV-infected individuals does not revolve around the initiation of highly active anti-retroviral therapy (HAART) and treating opportunistic infections only, but also to educate the individuals regarding harm reduction and HIV prevention.

Case Report

We described a case of a 36-year-old individual who was recently diagnosed with HIV with CD4+ T-cell counts of 8 cells/microL and started on HAART with Tenofovir/ Emtricitabine and Efavirenz.

After the initiation of HAART for two weeks, he was admitted with fever, lethargy and shortness of breath for 1 week duration. Physical examination revealed that he was febrile (39°C), lethargy looking, tachypneic with respiratory rate of 24 breaths per min, with no other significant physical findings.

The fever did not settle with intravenous ceftriaxone followed by piperacillin-tazobactam. All cultures and sputum for tuberculosis workup were negative. His chest radiography was normal (**Figure 1**) and a contrast-enhanced computed tomography abdomen showed only multiple enlarged intra-abdominal lymph nodes.

Physical examination after one week of antibiotic commencement revealed a new left cervical lymph node with size of 1cm x 1cm. Biopsy of the lymph node showed granulomatous tissue with positive

acid fast bacilli stain. Fundoscopy done as part of his fever workup revealed left eye cytomegalovirus (CMV) retinitis (**Figure 2**).

He was treated as immune reconstitution inflammatory syndrome (IRIS) with two new infections: tuberculosis (TB)-lymphadenitis and left eye CMV retinitis. Prior to initiation of HAART, his tuberculosis screening was negative, and he did not have any visual complaint.

Anti-TB therapy, intravitreous and intravenous ganciclovir were commenced. Despite on anti-TB for one month duration, his condition further deteriorated. He had poor appetite, lethargy, reduced weight and recurrent hypoglycaemia episodes. His liver function test was deranged, likely due to anti-TB medications. After multiple rechallenge, he was only able to tolerate anti-TB regime of isoniazid, oflaxacin and ethambutol. His random serum cortisol level was relatively normal despite him being ill. He was started on intravenous hydrocortisone, which improved his overall condition.

He subsequently had a prolonged stay in hospital for a total of eleven weeks.

Discussion

This case illustrated a HIV infected individual with a low CD4+ T-cell counts who had paradoxical effect to HAART and anti-TB medication.

Immune Reconstitution Inflammatory Syndrome (IRIS) refers to a collection of inflammatory related disorders that get paradoxical worsening with the initiation of HAART in HIV infected individuals.

HIV infected individuals who host opportunistic infection may have no clinical complaint and signs, possible due to the their poor host inflammatory and immune response. The opportunistic infections are unmasked after the commencement of HAART as there is rapid rise in CD4+ T-cell counts and drop in HIV viral load. Notermans's (1999) study reported that CD4+ T-cell counts would increase by a median of 170 to 420x10^6cells per liter over 2 years of successful potent HAART [1].

Ratnam (2006) reported that approximately one-quarter of individuals who were started on HAART experienced an IRIS event, in which the majority had dermatological symptoms, in particularly genital herpes and warts [2]. Most of the IRIS are self limiting, and rarely cause fatality if being managed properly. The timing of development of IRIS after HAART ranged between 4 to 186 days, with a median time of 29 days [3]. As for our case patient, he had IRIS two weeks after HAART.

There is no universal agreed-upon definition for IRIS. French (2004) suggested the following criteria to aid the diagnosis [4].

Major Criteria

1) Atypical presentation of "opportunistic infections (OI) or tumors" in individuals responding to anti-retroviral therapy.

2) Decrease in plasma HIV RNA level by at least 1 $\log_{10}$copies/mL.

Minor Criteria

3) Increase in blood CD4+ T-cell count after HAART.

4) Increase in immune response specific to the relevant pathogen

5) Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuous anti-retroviral therapy.

There are two forms of IRIS

A) Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of a treated disease after HAART.

B) Unmasking IRIS is a HAART-associated inflammatory manifestation of a subclinical infection with a hastened presentation [5].

Grant PM (2010) reported that the risk factors for IRIS are low CD4+ T-cell counts and higher HIV RNA levels at baseline, higher CD4+ T-cell counts and lower RNA level on treatment, and presence of fungal infections [6]. Another interesting study by Ratnam (2006) reported that the initiation of HAART at a younger age had increased risk for IRIS as young individuals are likely to have a greater immune restoration compared to elderly who had suboptimal CD4 cell response, discordant CD4 cell and virological response to HAART [2].

Our case patient had a cervical lymph node enlargement after initiation of HAART which lead to the diagnosis of tuberculosis (TB)-lymphadenitis. Dheda (2004) reported that the fatality risk was exceptionally high in individuals with tuberculosis and low CD4 count during the intensive phase of tuberculosis treatment. HAART was shown to reduce the mortality risk in tuberculosis and HIV co-infected individuals [7].

There are arguments regarding the timing of initiation of HAART in individuals with tuberculosis infection, particularly the concerns about the combined toxic effects of drugs, increased risk of IRIS, and poor adherence with increase in pill burden. The results of the CAMELIA trial supported the initiating of HAART two weeks after anti-tuberculosis therapy as it significantly increased the survival among HIV infected individuals. Francois-Xavier's study (2011) reported that the initiation of HAART early in tuberculosis treatment would increase the incidence of IRIS by a factor of 2.5, but the survival rate was still higher in earlier-HAART group compared to late initiation (8 weeks).[8] The death rate rose from 5.4 per 100 person-years to 12.1 per 100 person-years when initiation of antiretroviral therapy was delayed until the completion of tuberculosis therapy in Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial [9].

Our case patient significantly improved with intravenous hydrocortisone, which could be due to anti-inflammatory property of corticosteroid, undiagnosed hypocortisolism, TB-adrenal or other opportunistic infections of adrenal glands. Corticosteroid had been shown to reduce mortality in TB meningitis and TB pericarditis only [10]. Dooley (1997) reported that corticosteroid had significant short term but minimal long term benefits for individuals with TB-pulmonary or lymphadenopathy, and thus they are not regularly prescribed for TB-pulmonary [11].

Our case patient did not have any eye symptom prior to HAART, and CMV retinitis was an incidental finding during workup for fever. It occurred much more earlier than the reported median time of 2.9 years by Jabs et al 2002 [12]. Long term follow up is required as CMV immune recovery uveitis is a chronic inflammatory syndrome that may lead to vision-threatening complications such as proliferative vitreoretinopathy, posterior subcapsular cataracts, and severe postoperative inflammation [13].

Major guidelines recommends for the continuation of HAART in individuals who developed IRIS, with the exception of life-threatening illness such as airway obstruction. Routine use of anti-inflammatory agents or steroid is not recommended. Screening and treating opportunistic infections prior to HAART are important as IRIS may lead to detrimental and poor outcome. Preferably, HAART should be deferred for at least two weeks after treatment of opportunistic infections.

In terms of prognosis, Murdoch (2008) reported that severe and life-threatening IRIS was uncommon, with twelve individuals admitted and two deaths attributed to IRIS in his cohort study of 423 individuals newly started on HAART for six months duration [14].

The response of individuals towards HIV infection, progression, HAART and outcome varies and they are unpredictable. Majority (80%) of HIV infected individuals develop AIDS after 8-10 years of disease, 10% progress to AIDS within 3 years of disease, and the remaining may be asymptomatic for more than 10 years even in the absence of treatment [15]. It was postulated that latter group of HIV infected individuals have the host immune response that can contain HIV virus for longer duration.

O'Brien's (2004) meta-analysis study discussed the importance of host immune response and the different vulnerability of individuals towards HIV. His study also proposed the evaluation of HIV disease progression via identification of "AIDS restriction or susceptible genes" [16]. For instance, Sunil (2008) described that the HIV infected individuals with CCL3L1-CCR5 genotype had a better CD4+ T-cell counts recovery than others [17].

The main aim of HAART is to suppress the HIV viral load to a below assay detection level and to restore the immune function. Treatment failure with HAART is associated with increase in morbidity and mortality. The common causes of treatment failure are non-compliance, low baseline CD4+ T-cell counts, and drug resistance.

Recently, there are more research look into the possibility of host genetic variation that influence the response to HAART. Further studies in the human genetic and HIV viral polymorphisms would lead to new approaches and improvement in HIV treatment and HAART efficiency.

Figures

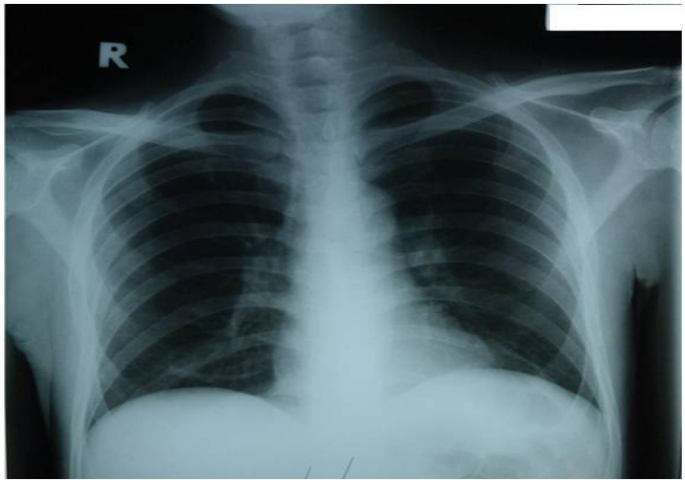

Figure 1 : Chest X-ray : Clear lung field, with no focal lesion.

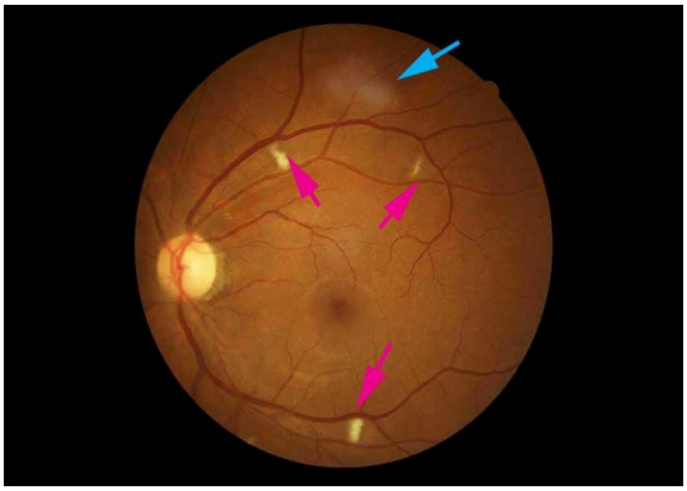

Figure 2 : Left eye with CMV retinitis

Blue arrow : The white patch with irregular border : CMV retinitis, Pink arrow : cotton wool spots

Conclusion

This case illustrates the potential of clinical deterioration of HIV-infected individuals after initiation of HAART and anti-TB, especially in those with extremely low CD4 count at presentation. Subclinical opportunistic infections may be unmasked with rapid increase in CD4+ T-cell counts and decrease in HIV viral load. Recognition of IRIS is crucial for institution of appropriate care and therapy to improve HIV infected individuals' outcome.

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