Unmasking tuberculosis-associated immune reconstitution inflammatory syndrome in HIV-1 infection after antiretroviral therapy

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Summary

The exaggerated immune response to the subclinical opportunistic microorganisms or their antigens can be found in HIV-1 infected patients after receiving antiretroviral (ARV) therapy. We report a case of unmasking tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in the HIV-1 infected patient who had no previous history of mycobacterial infection. She had tuberculosis of intestines, peritoneum and mesenteric glands within 2 months of ARV. However, her sputum acid-fast bacilli stain, sputum, blood and cervical lymph node aspiration cultures for mycobacterium were negative. Her CD4 cell count increased of from 46 cells/μL at baseline before receiving ARV to 155 cells/μL at month 6 of ARV. In addition, her plasma pro-inflammatory (IFN-γ and TNF-α) and anti-inflammatory (IL-10) cytokine measurement was supported the occurrence of immune restoration reaction. Therefore, the changing in these cytokine profiles may be an important marker of developing unmasking TB-IRIS. *(Asian Pac J Allergy Immunol 2010;28:206-9)*

Introduction

Restoration of the immune system after commencing antiretrovirals (ARV) resulting from a quantitative and qualitative process of cell immune activity recovery may evolve with adverse clinical phenomena, known as the immune reconstitution inflammatory syndrome (IRIS).[1-3] There are two forms of IRIS. The first being paradoxical deterioration in patients diagnosed with opportunistic infection and on antimicrobial treatment prior to starting ARV (paradoxical IRIS). The second being the unmasking of active opportunistic infection by ARV treatment that was unrecognized at the start of ARV because the patient was either asymptomatic or minimally symptomatic but presents soon after ARV initiation unmasked by the recovering immune system (unmasking IRIS).[4] *Mycobacterium tuberculosis* and non-tuberculous mycobacteria are pathogens that commonly provoke IRIS.[5-6] Tuberculosis-associated IRIS (TB-IRIS) usually occurred in patients starting ARV within two months of starting antituberculous therapy.[7] A longer duration (>2 months) of antituberculous therapy may lower bacterial load and its antigen that lead to decreasing the risk of TB-IRIS development.[8-9] We present a case of unmasking TB-IRIS who had no clinically evidence of *M. tuberculosis* infection at the time of ARV initiation.

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Case report

A 42-year-old woman was diagnosed as being HIV-1 positive in April 2007 and started treatment with GPO-VIR Z250 (Zidovudine + Lamivudine + Nevirapine). At month 2 of ARV, she had tuberculosis of intestines, peritoneum and mesenteric glands. She had fever, dyspnea and no previous history of mycobacterial infection. In addition, two sputum samples collected for acid-fast bacilli stain and culture were negative during the appearance of her clinical symptoms. Without termination of ARV, she began antituberculous therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. At 4 months of ARV, she was admitted with abdominal and joint pain, nausea and cervical lymphadenitis. During hospitalization, blood and cervical lymph node aspiration for mycobacterial culture were performed. Both cultures were sterile after 6 and 8 weeks of incubation respectively. Her CD4 count was dramatically increased during the follow up (from 46 cells/μL at baseline to 155 cells/μL at month 6 of ARV). At the end of month 4 of ARV, the patient was treated with prednisolone (2 tablets 5 mg three times daily) in addition to antituberculous agents and ARV. Her clinical symptoms gradually improved and complete recovery occurred after 7 months from her clinical event. It is likely that she had unmasking TB-IRIS. Therefore, her plasma pro-inflammatory cytokines (IFN-γ and TNF-α) and anti-inflammatory cytokine (IL-10) were measured retrospectively using ELISA kits (IFN-γ, BioSource Europe SA, Nivelles, Belgium, with a sensitivity of 0.03 IU/mL; TNF-α and IL-10, Immunotech, Beckman Coulter, Marseille, France, with a sensitivity of 5 and 10 pg/mL, respectively) and compared to four patients with previous history of *M. tuberculosis* infection without IRIS as a control. At baseline before starting ARV, the level of plasma IFN-γ of this patient was not different from the controls however the levels of TNF-α and IL-10 were higher than those observed in the controls (Figure 1A-C). In the first month of ARV, the level of IFN-γ was increased beyond the normal range (0-0.89 IU/mL). Then its level was rapidly decreased close to the control level in the third month following by a slow decrease to the control level (<0.03 IU/mL) at month 6 (Figure 1A). Although, the levels of TNF-α and IL-10

were decreased to control level by 3 months of ARV, the level of IL-10 was more rapidly decreased (Figure 1B and 1C). After administration of prednisolone (2 tablets 5 mg three times daily), the level of IFN-γ remained constant at <0.03 IU/mL (Figure 1A) while the levels of TNF-α and IL-10 were slightly increased (Figure 1B and 1C). Therefore, the condition of a higher pro-inflammatory (IFN-γ and TNF-α) and a lower anti-inflammatory (IL-10) was resulted in the imbalance of the cytokines favoring the inflammatory partway which leading to unmasking TB-IRIS.
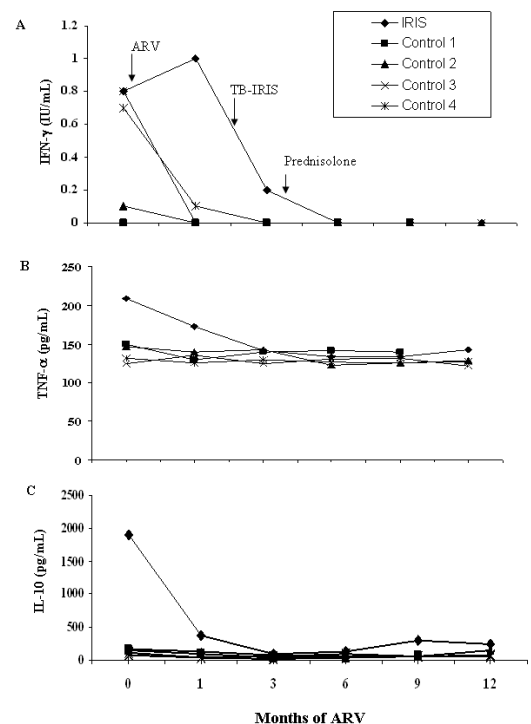

Figure 1. The plasma pro-inflammatory IFN-γ(A) and TNF-α(B) and anti-inflammatory IL-10 (C) cytokine profiles in a patient who developed unmasking TB-IRIS and controls after ARV initiation.

Discussion

IRIS has been postulated to be caused by an enhanced immune response to previously subclinical infections. However, the unmasking IRIS can develop also in patients with no previous history of opportunistic infections, since the restored immunity might respond to the subclinical opportunistic infection or other yet undefined antigens. In the present study, the patient had no previous history of active

pulmonary *M. tuberculosis* infection. Thus the patient was treated with ARV without any delay. The rapid increase of CD4 cell count from 46 to 155 cells/µL (3.37 times) during 6 months of ARV was observed. During this time, the patient developed abdominal and joint pain and cervical lymphadenitis indicated the inflammatory reaction resulted from the restoration of the immune functions. In addition, the plasma pro-inflammatory (IFN-γ and TNF-α) and anti-inflammatory (IL-10) cytokines measuring during the follow-up period confirmed the inflammatory response. IFN-γ has been demonstrated to be a major effector cytokine in human host responses against tuberculosis.[10] It is produced mainly by T lymphocytes of both CD4+ and CD8+ cell type, and it stimulates macrophage function in a variety of ways, including increasing production of both reactive oxygen and reactive nitrogen species that are implicated in intracellular killing or growth inhibition of *M. tuberculosis*. A number of studies showed that a high level of IFN-γ transcription was observed before ARV and decreased during ARV.[11-13] Thus, the increased level IFN-γ at the first month of ARV in the patient with TB-IRIS may indicate the presence of subclinically *M. tuberculosis* infection. A higher level of plasma IFN-γ and a lower level of IL-10 may also play a role in development of TB-IRIS, since the imbalance of these cytokines has been observed in peripheral blood mononuclear cells (PBMCs) of TB-IRIS patients.[14] IL-10 is an anti-inflammatory cytokine which inhibits the expression of TNF-α known as a pro-inflammatory cytokine to keep a balance in immune response in normal human being.[15-16] In the present study, we found that the IL-10 level of the patient with unmasking TB-IRIS at baseline was almost fifteen times higher than the controls and then dramatically decreased close to the control level within the first month. In the same period of time, the level of TNF-α slowly decreased and remained at a higher level than the control after the first month of ARV. Thus, the imbalance between IL-10 and TNF-α may associate with the disruption of regulatory T-cells signaling and leading to developing of IRIS.[17-18]

In conclusion, the unmasking TB-IRIS can be developed in patients with no previous history of mycobacterial infections. Therefore, the changing of plasma pro-inflammatory (IFN-γ and TNF-α) and anti-inflammatory (IL-10) cytokine profile during the first three months of ARV may be an important marker of the developing unmasking IRIS.

Acknowledgements

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