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Disseminate and fatal cytomegalovirus disease with thymitis in a naive HIV-patient after early initiation of HAART: Immune restoration disease?

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Abstract

We describe a naïve HIV-infected patient who developed a *Pneumocystis carinii* pneumonia and disseminate and fatal cytomegalovirus disease within 3 months after initiation of HAART, suggesting due to coincidence in time, an immune restoration disease. We propose an alternative hypothesis.

Keywords: Immune restoration disease; Thymitis cytomegalovirus; AIDS

1. Introduction

HIV-patients under HAART may experience severe systemic inflammatory reactions that have been defined as immune restoration disease (IRD). It has been communicated that IRD has two different patterns; an earlier pattern during the first 3 months of HAART as an immune response against viable opportunistic pathogens, and a later pattern as an immune response against non-viable opportunistic pathogens months to years after HAART (French et al., 2004). During the IRD, a baseline CD4 cell count below 100 cells/mm^3 has been reported among patients, while after HAART an increase above 200 cells/mm^3 is reached (Price et al., 2001). Outcomes range from minimal morbidity to fatal progression (French et al., 2004; Hirsch et al., 2004). In this way, atypical presentations of mycobacterial, cytomegalovirus (CMV), hepatitis B virus, hepatitis C virus and JC virus have been described after initiating HAART (French et al., 2004; Safdar et al., 2002).

We here report the case of a naïve HIV-infected patient who developed *Pneumocystis carinii* pneumonia as well as disseminated and fatal CMV infection coinciding with the initiation of HAART.

2. Case report

In 1993, a 32-year-old woman was diagnosed of HIV infection in our unit. Then, her CD4 T cell count was 840 cells/mm^3, and HIV plasma viral load (pVL) was above 75,000 copies/mL. The moment that primoinfection occurred in the past was unknown because it was asymptomatic. Since she declined to receive antiretroviral therapy, a progressive CD4$^+$ T cell count decrease was taking place during the following 9 years. In July 2002, she began HAART with zidovudine, lamivudine, and abacavir, having HIV pVL above 75,000 copies/mL, CD4$^+$ T cell count of 90 cells/mm^3, and a thymic volume (measured by mediastinic computed

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tomography) of 1.2 cm^3. In the next 3 months after the initiation of HAART, the patient developed several infectious events such as *P. carinii* pneumonia after 10 days, which was successfully treated with cotrimoxazole. Seven days later, the patient showed low level of conscience, convulsions, and plasmatic Na^+ concentration of 102 mequiv./L, recovering from the neurological events after hiponatremia treatment. Three weeks after the initiation of HAART, a colonoscopy was performed due to the development of mucosanguineous diarrhoea. The biopsy of the colon revealed cytomegalic inclusion bodies that allowed the diagnosis of CMV colitis, which was treated with ganciclovir and foscarnet, while HAART was interrupted after 6 weeks of its initiation due to an apparent IRD. She had not previously suffered a CMV-related disease, thus, she did not take ganciclovir or foscarnet. Despite of this new treatment, symptoms as fever, cough, and disnea turned up, as well as bilateral interstitial infiltrate, which was evidenced by chest radiography. Since the patient treated with ganciclovir and foscarnet showed favourable evolution, empiric CMV pneumonia was diagnosed. Ten days later, the patient referred lost of vision and fundus ophthalmoscopic examination confirming CMV retinitis, despite the treatment she had taken. At that moment, CMV plasma viral load was above 738,000 copies/mL, it was not possible to achieve the sequence of CMV strain to study the development of drug related resistance to ganciclovir and foscarnet, so, due to the progression of CMV disease with this drugs we decided to switch to cidofovir.

Since the patient progressed with adverse clinical events, IRD was ruled out and a new HAART regimen including zidovudine, lamivudine, and lopinavir/ritonavir was prescribed. Finally, although CD4 T cell count increased to 432 cells/mm^3 and CMV viral load decreased to 1000 copies/mL, the patient developed fatal meningoencephalitis after 12 weeks of initiation of HAART. Necropsy was performed to further studies.

3. Material and methods

Plasma HIV-1 RNA was measured by a quantitative PCR (HIV Monitor Test kit version 1.5, Roche Molecular System Inc., Branchburg, NJ) according to the manufacturer's instructions. This assay has a detection limit of 50 HIV-1 copies/mL. Frozen plasma samples stored since 1993 were used to measure CMV viral load by a quantitative PCR (Cobas Amplicor CMV Monitor test, Roche Molecular Systems Inc., Branchburg, NJ) according to the manufacturer's instructions. This assay has a detection limit of 400 CMV-DNA copies/mL. Total CD4 cell count was determined in fresh samples by conventional flow cytometry.

Since the patient was enrolled in a study about the role of the thymus in T cell repopulation, the following measured parameters were available: mediastinic computed tomography that was performed with a modified method as previously described (Choyke et al., 1987); and the quantification of

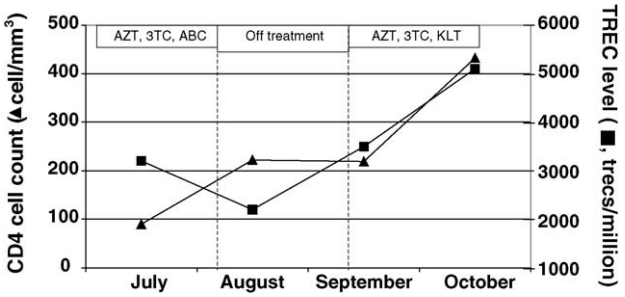

Fig. 1. Evolution of total CD4 cells counts and TRECs.

TRECs generated during the rearrangement of T cell receptor genes as one proposed molecular marker for the determination of recent thymic cell emigrants. A PCR-based method for quantifying δRec-ΨJα TREC number has been described (Douek et al., 1998).

4. Results

Evolution of total CD4 cell counts and TRECs are showed in Fig. 1. Thymic volume was 1.2 cm^3 (score 2), which has been related with an attrofic thymus and fat infiltration.

Evolution of plasma viral load VIH and CMV are showed in Fig. 2. Plasma viral load CMV was measured in blood samples since year 1993 and it revealed that CMV was detectable in plasma 2 months before starting HAART. It increased until 738,000 copies/mL after initiating first HAART regimen. Despite of second HAART and therapy with ganciclovir, foscarnet and cidofovir were started, CMV was always detectable in plasma.

4.1. Necropsy

It was procedure as a standard autopsy, with special looking for thymic remnants. Immunohistochemical thymus studies were performed by streptavidine-biotine technique for CD3, CD20 (Dako-labs), CD4, CD8, CD5 (Vitro labs), and pan-cytokeratins (Menarini lab) antibodies, on paraffin embedded sections. The scarce lymphocytes presents were

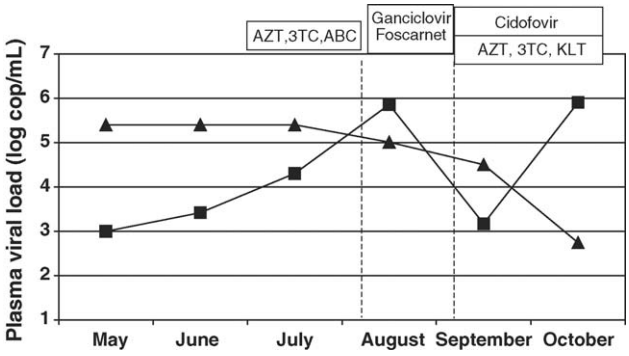

Fig. 2. HIV and CMV plasma viral load evolution. (■) Plasma viral load CMV; (▲) plasma viral load HIV.