NEW MICROBIOLOGICA, **30**, 283-285, 2007

Virological responses in a patient with recent HIV-1 infection experiencing an EBV reactivation

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SUMMARY

The dynamics of interactions between HIV and other viral agents and their reciprocal influence on the cellular immune response is not fully understood.
A clinical report is here described regarding an EBV reactivation occurring during a recent HIV infection. The two viruses appear to act in a sequential manner, mutually influencing each other in their replication and leading to determine a clinical outcome in the patient under study.

KEY WORDS: EBV, HIV, Primary HIV infection (PHI), Coinfection, Immune system activation

Herpesviruses and HIV coinfections are frequently observed in clinical practice.
The very high occurrence of Epstein-Barr virus (EBV)-related diseases in patients with HIV infection has been strongly documented, so that many of them are commonly referred to as AIDS-defining events.
Several efforts have been done to better define EBV-host interactions and there is growing evidence that the change from self limiting infection to a more serious disease is due to the loss of surveillance by the immune system.
Patients with AIDS have 10 to 20 times more circulating EBV-infected B cells than healthy persons (Birx *et al.*, 1986), likely due to a T cell impairment in suppressing EBV-infected cells. A decline in EBV-specific cytotoxic T cells and an elevated and increasing EBV-viral load preceding the development of EBV-associated non Hodgkin lymphoproliferative diseases has been described during HIV infection (Kersten *et al.*, 1997).
Further complexity emerges in the presence of primary HIV infection (PHI) hallmark of which is an intense and chaotic immune activation. PHI indeed represents a clinical condition in which the massive HIV replication is counterbalanced by the immune system's efforts in containing viral diffusion through cellular activation: although a host-favourable equilibrium is generally achieved, temporary immune depression cannot be avoided.
We here describe the case of a patient experiencing PHI: immune dynamics underlying acute infection seem to be sequentially and mutually influenced by EBV and HIV infection.
A 38 years old homosexual male came to our attention because of a symptomatic PHI in October 2003. Due to his good immunovirological parameters (CD4 T lymphocytes: 799 cells/µl, HIV-RNA: 1569 copies/ml) antiretroviral therapy was not initiated. After a 3 month period characterized by a substantial absence of symptoms and persistence of good CD4 T cell and HIV-RNA values, we observed a sudden worsening of the

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clinical status with appearance of elevated fever, fatigue, anorexia and pharyngitis associated with a sharp increase of HIV plasma viremia (Figure 1) and a strong decrease of CD4 T cell percentage. Due to a significant alteration of the differential, showing a relative lymphocytosis, and the sudden increase of HIV viremia, infection by a new viral agent was hypothesized and serologic tests for EBV infection were performed. A high titer of viral capsid antigen (VCA) IgM antibodies was found, clearly indicating an infection sustained by EBV, resembling infectious mononucleosis.

To better characterize this concomitant infection, likely due to reactivation of a previously achieved EBV-related infection, soon after the appearance of positive VCA IgM antibody index, the patient was scheduled for sequential weekly venous blood samples, after his informed consent. HIV-RNA and EBV-DNA were determined in plasma (expressed as copies/ml), along with cell-associated HIV-DNA and EBV-DNA in peripheral blood mononuclear cells (PBMC) (expressed as copies/10^5 PBMC). HIV-DNA and EBV-DNA in cells and in plasma were quantified with a Real Time PCR, based on TaqMan technology, whereas HIV-RNA in plasma was assessed by means of the branched DNA assay.

Ten days following the peak of HIV-RNA mentioned above, viral replication was contained and HIV-RNA dropped back to low levels (in 21/1/2004) (Figure 1); this was mirrored a week later by a small modulation of HIV-DNA, but a sharper increase of EBV-DNA in PBMCs (Figure 1). Conversely, EBV plasma viremia remained undetectable during the whole observation period. Both cellular EBV-DNA and HIV-DNA measured in subsequent time frames resulted undetectable (Figure 1); this finding was associated with the presence of an EBV-specific CTL response, determined through tetramer technology (data not shown). The patient's follow-up documented a rapid restoration of excellent clinical conditions with maintenance of good immunovirological parameters which did not require initiation of antiretroviral therapy till the present time. Of note, EBV-VCA IgM antibodies remained elevated, though slightly declining, for a 2-year period.

This case report presents an *in vivo* model of the possible clinical interaction between an herpes virus and a retrovirus during PHI. Providing a change of perspective, HIV-1 seems to act as an opportunistic pathogen, probably taking advantage of its tropism for activated T lymphocytes responding to the EBV-infected B cells.

Looking at the levels of EBV viremia (Figure 1), we assume an EBV infection remaining latent for a long time prior to the HIV-1 seroconversion. At the time of HIV infection, we believe both viruses took advantage of the progressive activation of the immune system, which had to face the alternate replication of the two pathogens.

Herpes virus reactivation probably occurred because of the transient immune system impairment due to PHI: a lower function of EBV-specific T cells in HIV-infected subjects could be related to a lack of a specific CD4 T cell help

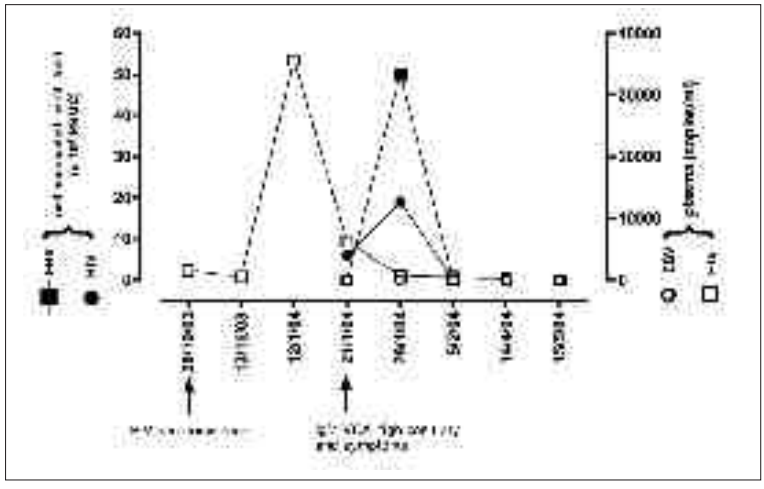

FIGURE 1 - *Virological parameters of both HIV and EBV in cell-associated and plasma samples.*

(Piriou *et al.,* 2005). The strong lymphocytosis induced by EBV, as previously reported by others (Cohen, 1986), could have been exploited by HIV for its replication (Moriuchi *et al*., 2000). Moreover, an increased susceptibility to HIV in EBV infection has been attributed to an enhanced expression of CCR5, the major coreceptor for HIV, on CD4 T lymphocytes (Moriuchi *et al*., 2003). Activation of the immune system, sustained by the elevation of HIV viremia in plasma, could have in turn promoted herpes virus reactivation, as evidenced by the increase of EBV-DNA in PBMC.

The rapid decrease of both plasma and cellular HIV viremia, the maintenance of a good CD8 specific response against EBV, the absence of EBV plasma viremia and the rapid clearance of the herpes virus in PBMC along with the prompt remission of symptoms, have been correlated to a favourable clinical outcome of HIV infection and could evidence a good control on both viruses by the patient' s immune system. Investigation of the role of EBV-DNA in monitoring EBV reactivation in immunocompromised patients appears to be crucial issue.

To our knowledge, few articles provide clinical and virological observations in patients experiencing a recent HIV seroconversion and a concomitant EBV infection (Moriuchi *et al.*, 2000). Besides describing the course of coinfection from the appearance of early symptoms, the case herein described is particularly remarkable because the data are not influenced by the presence of antiretroviral therapy.

Finally, from a clinical point of view, much attention should be posed on the monitoring of HIV-infected patients undergoing superinfections by other viral agents or their reactivation.

REFERENCES

Birx, D.L., Redfield, R.R., Tosato, G. (1986). Defective regulation of Epstein-Barr virus infection in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related disorders. *New England Journal of Medicine,* **314** (14), 874-879.

Cohen, J.I. (2000). Epstein-Barr virus infection. *New England Journal of Medicine,* **343** (7), 481-492.

Kersten, M.J., Klein, M.R., Holwerda, A.M., Miedema, F., Van Oers, M.H. (1997). Epstein-Barr virus-specific cytotoxic T cell responses in HIV-1 infection: different kinetics in patients progressing to opportunistic infection or non-Hodgkin's lymphoma. *Journal of Clinical Investigation*, **99** (7), 1525-1533.

Moriuchi, M., Moriuchi, H., Williams, R., Straus, S.E. (2000). Herpes simplex virus infection induces replication of human immunodeficiency virus type 1. *Virology,* **278** (2), 534-540.

Moriuchi, M., Moriuchi, H. (2003). Increased susceptibility to HIV-1 of peripheral blood lymphocytes in acute infection with Epstein-Barr virus. *Journal of Medical Virology*, **71** (3), 343-346.

Piriou, E.R., Van Dort, K., Nanlohy, N.M., Van Oers, M.H., Miedema, F., van Baarle, D. (2005). Novel method for detection of virus-specific CD41+ T cells indicates a decreased EBV-specific CD4+ T cell response in untreated HIV-infected subjects. *European Journal of Immunology* **35** (3), 796-805.