New Microbiologica, **38**, 289-292, 2015

Durable viral suppression in an HIV-infected patient in the absence of antiretroviral therapy

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SUMMARY

We describe the case of a young woman with an acute HIV infection characterized at onset by neurological features. The patient spontaneously controlled her HIV infection and recovered in a short period of time.
The patient's clinical and virological history showed a peculiar evolution of HIV infection, with an MDR HIV-1 in CSF and a wild HIV strain in PBMCs. The patient's PBMC showed a rapid shift from a wild type to an MDR strain in few days.

KEY WORDS: HIV, neurological features, transmission events, elite suppressor.

Received January 19, 2015 *Accepted* March 2, 2015

CASE REPORT

Acute HIV infection may present as a mononucleosis type of syndrome with a constellation of nonspecific symptoms, detectable in only 50-70% of infected patients (Schacker *et al.,* 1996). A limited number of cases may present neurological features, such as aseptic meningitis, encephalitis, meningoencephalitis, often associated with a more rapid progression to AIDS (Castellanos *et al.,* 1994; Hassin-Baer *et al.,* 1998; Boissé *et al.,* 2008; McArthur *et al.,* 2005; Andrade *et al.,* 2014).
We describe a case of HIV-correlated meningoencephalitis in a young woman, who has spontaneously controlled her HIV infection from seroconversion to date, in the absence of antiretroviral therapy.
A 19-year-old woman was admitted to the Infectious Diseases Operative Unit in July 2008. The patient showed fever (39°C), severe lethargy, neck stiffness and pyramidal signs. Electroencephalogram analysis recorded a strong depression of cerebral electric activity and nuclear magnetic resonance indicated inflammation in the supratentorial and subtentorial leptomeninges. The metabolic panel showed normal values. The percentage of lymphocytes and monocytes was significantly increased as was C-reactive protein.
Cerebrospinal fluid (CSF) analysis disclosed pleocytosis with an increased white blood cell count (35 cells/mmc) and modified protein levels (2.78 g/L). Direct microscopic examination and further cultures ruled out bacteria and fungi. Cryptococcus antigen was also negative as was the detection of antibodies (IgM and IgG) to *Borrelia burgdorferi* and West Nile Virus. In addition, PCR analysis excluded CMV, EBV, HSV-1/2, VZV, Enterovirus, Adenovirus and JCV. All blood cultures showed negative results.

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Due to a strong suspicion of acute meningoencephalitis of unknown origin, the patient was empirically treated with ceftriaxone, ampicillin, acyclovir and dexamethasone. The day after hospitalization, her plasma sample was also analyzed for HIV infection. A diagnosis of acute HIV infection was established by a positive fourth generation test, a serum reactivity to only HIV p24 and p55 and a low level of avidity index (0.3 OD) (Re *et al.,* 2012). T lymphocytes [T CD4+ 740/mmc (25%), CD8+ 1540/mmc (52%)] showed an inversion of the CD4/CD8 ratio and viral load and HIV RNA load was assessed at $3.6x10^3$ copies/ml (Figure 1).

Further history-taking identified the patient's partner, a 20 year-old male, vertically infected at birth and already followed by the Infectious Disease Unit, suggesting a sexual transmission, even though the two patients referred constantly protected sexual intercourse. The case patient's partner had a complex clinical history, with several therapeutic approaches for accumulating resistance-correlated mutations and, at the time of this finding, he presented an elevated blood viral load ($1x10^4$ HIV-RNA copies/ml).

Since HIV-1 RNA from our patient's plasma was not amplified, probably due to suboptimal sample storage, proviral DNA, successfully obtained from blood PBMCs, revealed wild type HIV-1 B subtype (R5 tropic virus) without any drug resistance mutations. Meanwhile, a multidrug-resistant R5 HIV with several mutations inducing resistance to all NRTIs, NNRTIs and PIs was detected in the CSF.

To support the clinical investigation, we reconstructed the transmission events by a specific dataset, including 7 HIV-1 *pol* gene isolates (3 from female and 4 from male sequences at different time points) previously classified as B subtype, 37 HIV-1 B subtype "local controls" and 57 subtype B reference sequences (Bon *et al.,* 2010; Falasca *et al.,* 2014). The dataset sequences were aligned and the best fitting nucleotide substitution model selected (Lo Presti *et al.,* 2012; Ciccozzi *et al.,* 2012).

Time-measured phylogeny and evolutionary rates were inferred using a Bayesian Markov Chain Monte Carlo (MCMC) approach (Beast version 1.8.0 http://beast.bio.ed.ac.uk) (Drummond *et al.*, 2005) implementing a GTR + I + G model. The MCMC was run until convergence was achieved on the basis of the effective sampling site (ESS). Only ESS values >250 were accepted.

The Bayesian Skyline Plot (BSP) demographic model under a relaxed (uncorrelated log normal) clock was selected on the basis of Bayes'

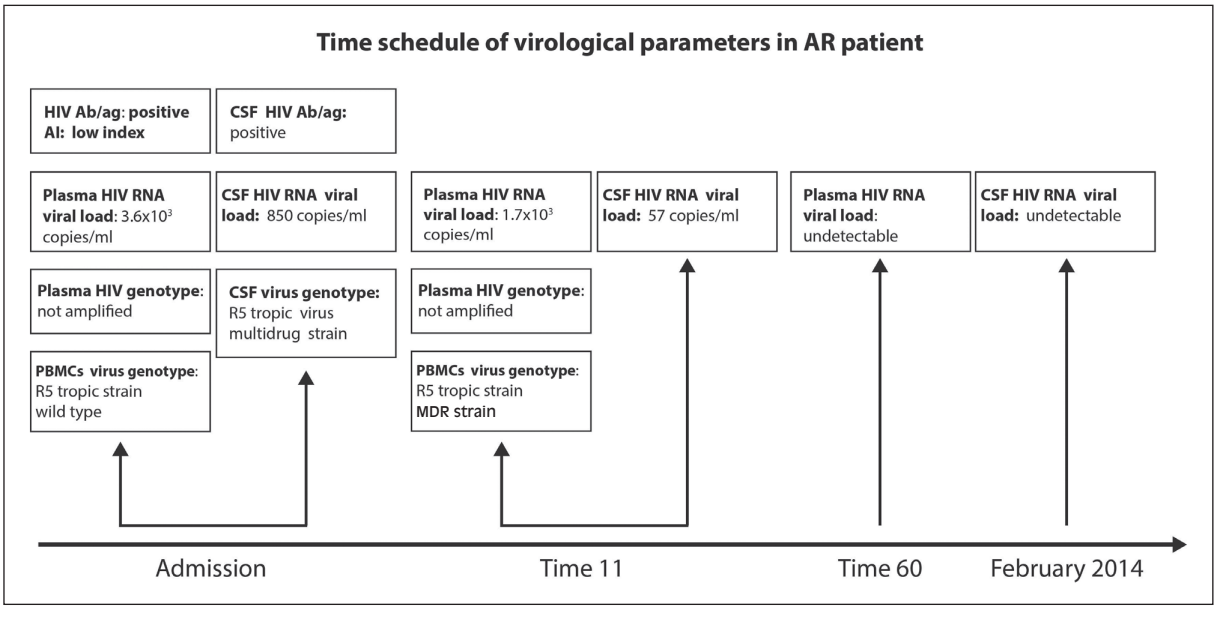

FIGURE 1 - *Time schedule of virological parameters in our patient from admission to date.*

Factors (2 ln BF >55). Using both "reference sequences" and "local controls", the Bayesian phylogenetic tree showed that the patient's isolates formed a significant monophyletic cluster (posterior probability =1) (Figure 2). The male sequence labelled as 48@08 was at the root of the female's sequences. The node connecting the female sequences (labelled as 49@08, 45@08, 44@08) showed a 95% HPD tMRCA estimate of 2004-2008.8. Besides confirming the transmission event and the direction of the transmission, our results estimated the date of the transmission event with good approximation between June and August 2008.

Eleven days post-admission, our patient's blood and CSF samples showed 1700 and 57 HIV copies/ml respectively (Figure 1). In addition, viral characterization performed PBMCs showed a shift from a wild HIV to MDR HIV-1 strain, with the same aminoacid changes present in the CSF sample. Since the patient showed a good state of health and favourable laboratory parameters (HIV RNA constantly undetectable and lymphocyte T CD4+ cell count at 1722/mmc), the medical staff decided not to initiate antiretroviral therapy and to check the patient at short intervals of time.

Further controls (at time 60 and afterwards) confirmed a lack of viral replication and optimal values of lymphocyte T CD4+ cell count. Both these parameters, in addition to a good overall health condition, confirmed the decision not to start antiretroviral therapy.

DISCUSSION

We reported the case of a young female patient with an acute infection characterized by an HIV wild type in PBMCs and an MDR HIV in cerebrospinal liquid. Despite the presence of neurological symptoms at onset, often classified as a

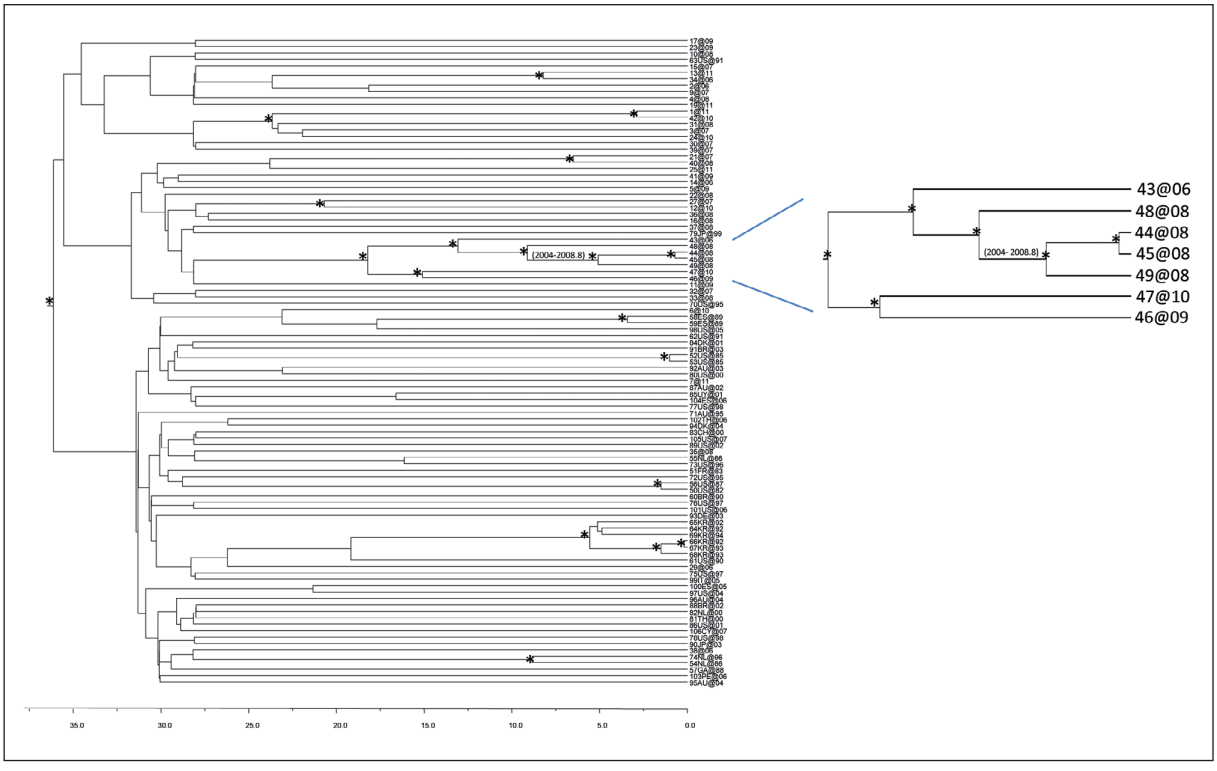

FIGURE 2 - *Bayesian phylogenetic tree of 101 HIV-1 subtype B Pol sequences implementing a relaxed molecular clock. The transmission event is evident in bold. The asterisks (*) along a branch represent significant statistical support for the cluster subtending the branch (posterior probability >98%). The time of the most recent common ancestor (tMCRA), and the credibility interval based on 95% highest posterior density interval (95% HPD) are also reported.*

negative marker, the patient rapidly recovered and showed a complete remission of the neurological picture. Moreover, the clearance of viral load and the assessment of optimal CD4 cell levels were achieved without antiretroviral therapy. Interestingly the HIV-1 strain isolated from CSF was an MDR strain with a large set of mutations able to escape most antiretroviral compounds and the HIV isolated in PBMCs showed a shift from a wild HIV to HIV-1 MDR tropic strain in few days.

Despite the absence of specific antiviral therapy, HIV disease progression was not accelerated and plasma viral load clearance was achieved and has been maintained, at least to date (six years later from onset), suggesting that our patient might be considered an elite non progressor.

Even if we are aware that host factors and low fitness of the MDR variant might play a crucial role in determining a non progressive evolution of the disease, the great benefits of early antiretroviral therapy, also assessed by recent guidelines (Antinori *et al.,* 2011), must not be underestimated.

The work was performed at the Microbiology Section of the *Department of Experimental, Diagnostic and Specialty Medicine, School of Medicine, University of Bologna, Italy*

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