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Onset of HIV-1 antibody production after highly active antiretroviral therapy in a seronegative HIV-1-infected child

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Individuals infected with HIV-1 develop specific antibodies against the virus. HIV-1 antibodies rarely fall to undetectable levels in the late stage of the disease, and their absence has been described in a few HIV-1-infected adults who rapidly progressed to AIDS after primary infection [1]. The reappearance of HIV-1 antibodies was recently observed in an adult after treatment with highly active antiretroviral therapy (HAART) [2]. We here report the case of a seronegative HIV-1 perinatally infected child who rapidly progressed to AIDS, in whom HIV-1-specific autochtonous antibody production occurred after HAART.

This female child was admitted to the Paediatric Department of Padova University at 12 months of age. According to her clinical records, she was born to an HIV-seropositive mother and was diagnosed as HIV-1 infected at 2 months of age by the detection of HIV-1 DNA using a polymerase chain reaction (PCR) assay (HIV-1 Amplicor, Roche Diagnostic Systems Inc., Branchburg, NJ, USA). At admission, her CD4 cell count was 170 cells/μl, and the plasma HIV-1 RNA content was over 6.0 $\log_{10}$ copies/ml (HIV-1 Amplicor Monitor, Roche) (Fig. 1a). Serological analyses, employing an enzyme-linked immunoabsorbent assay (ELISA; HIV-1/HIV-2, Ortho Diagnostics, Raritan, NJ, USA), a particle agglutination test (HIV-1/HIV-2 Serodia, Fujirebio Inc., Tokyo, Japan), and Western blot (HIV blot 2.2, Genelabs Diagnostics, Singapore) disclosed that the child lacked antibodies to HIV-1 (Fig. 1b). The child showed HIV-1-related neurological symptoms, and was classified as C3 according to the Centers for Disease Control and Prevention criteria [3].

Fig. 1

Fig. 1

At 13 months of age, HAART (lamivudine 35 mg twice a day, zidovudine 70 mg twice a day, plus nelfinavir 250 mg three times a day) was started. After 8 weeks' treatment, the plasma HIV-1 RNA level decreased by only 0.7 $\log_{10}$, CD4 lymphocytes increased from 170 to 570 cells/μl, and thereafter remained at levels ranging from 460 to 750 cells/μl despite the persistence of a high HIV-1 RNA load (Fig. 1a). Serological analyses during the first 2 months of HAART confirmed the lack of HIV-1 antibodies, and excluded the possibility that HIV-1 seronegativity was caused by quantitative deficiencies in serum immunoglobulin (Ig), as Ig levels were within or even above the normal range [IgG 14.30 g/l (normal range 5.20-10.80 g/l), IgA 1.22 g/l (normal range 0.45-1.35 g/l), IgM 2.16 g/l (normal range 0.52-2.00 g/l)]. An in-vitro antibody production assay [4] carried out at 14 months of age revealed a high level of spontaneous Ig synthesis (3.24 μg/ml, normal range 0.025-0.170 μg/ml), which decreased after pokeweed mitogen (PWM) stimulation (1.9 μg/ml, normal range 0.4-23 μg/ml), thus indicating a dysregulation of the B cell compartment [4]; no in-vitro synthesis of either spontaneous or PWM-induced HIV-1-specific antibodies was detected. Three months after starting HAART, agglutination test findings were positive for HIV-1 antibodies; Western blot analysis disclosed antibodies against gp120/gp160 Env proteins, and weak seroreactivity against p24 Gag protein. Serological analyses during follow-up confirmed the persistence of a strong seroreactivity against gp120/160, but failed to detect antibodies against other HIV-1 viral proteins, and the Western blot profile did not meet the criteria for HIV-1 seropositivity (Fig. 1b). At 24 months of age, serum Ig levels (IgG 15.50 g/l, IgA 1.71 g/l, IgM 1.51 g/l) were similar to those observed at the beginning of HAART. Although in-vitro antibody production assays showed an overall decrease in spontaneous (1.9 μg/ml) and PWM-induced (0.8 μg/ml) Ig production, HIV-1-specific antibodies were detected both in the absence and presence of PWM (12 and 6 arbitrary units, respectively; lower limit of detection 3.9 arbitrary units). The child was clinically stable during follow-up, and showed moderate neurological improvement.

In infants with perinatally acquired infection, autochtonous antibody production usually occurs within 3-6 months of life [5]. Early infection in the lymphoid organs, resulting in severe T cell depletion and exposure to high amounts of HIV-1, possibly leading to B cell anergy, might explain the lacking humoral response to HIV-1 in this child. After HAART, the plasma HIV-1 RNA load did not decrease significantly, but immune system functions appeared to be partly restored, as suggested by the CD4 cell increase, and the decreased in-vitro synthesis of total Ig, which may account for the onset of humoral response to HIV -1. Interestingly, the pattern of HIV-1 seroreactivity remained restricted mainly to gp120/gp160. This could reflect the incomplete restoration of immune functions, as also suggested by the finding that in-vitro synthesis of total Ig and HIV-1-specific antibodies did not increase after PWM stimulation.

In conclusion, this case suggests that, even in the advanced stage of disease and in the absence of a consistent antiretroviral effect, HAART may partly restore the immune system, and enable it to generate a humoral response against several HIV-1 epitopes. That the seroreactivity pattern did not fulfill the current criteria for HIV-1 seropositivity urges caution in interpreting serological results in patients who seroconverted during HAART.

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