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BRIEF REPORT

HIV-2 Primary Infection in a French 69-Year-Old Bisexual Man

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More than 1 million individuals, mainly in West Africa, are thought to be infected with HIV-2. Acute HIV-2 infection is rarely observed, only 2 primary infections have been described to date. We report a detailed case of HIV-2 primary infection in a 69-year-old French bisexual Caucasian man, thereby providing valuable insights into HIV-2 early infection.

Keywords. early treatment; HIV-2; primary infection; reservoir.

CASE REPORT

A 69-year-old French bisexual Caucasian man with no significant prior medical history and no travel history presented to Brive-La-Gaillarde Hospital in mid-April of 2017 (visit 1 [V1]), with a 1-month history of upper respiratory tract symptoms, low-grade fever, fatigue, and a positive HIV serology performed 2 weeks prior using a fourth-generation enzyme-linked immunosorbent assay (ELISA; HIV Combi, Cobas, Roche Diagnostics GmbH, Mannheim, Germany). Three weeks before V1, he exhibited a generalized maculopapular rash that lasted for 3 days. He reported no history of diarrhea or weight loss. Clinical examination revealed no signs of pharyngitis, fever, adenopathy, or organomegaly. Chest radiography yielded normal chest findings. He reported having engaged in unprotected anal and oral sexual encounters with 15 male individuals between March of 2016 and April of 2017. Three of these individuals had been unknown to him, and none of them came from HIV-2-endemic areas in West Africa. His last at-risk exposure occurred 5 weeks before, in mid-March 2017, with an unknown individual, with whom he engaged in unprotected receptive anal intercourse that involved ejaculation and unprotected mutual oral sex. The patient had a negative HIV serology 1 year before presentation. Screening for other sexually transmitted infections (syphilis, hepatitis B virus, hepatitis C virus, *Neisseria gonorrhoeae,* and *Chlamydia trachomatis*) was negative.

At V1, HIV infection was confirmed by a fourth-generation HIV ELISA assay (HIV Ag/Ab Combo, Architect, Abbott, Wiesbaden, Germany), detecting anti-HIV-1 and anti-HIV-2 antibodies, and HIV-1 p24 antigen (p24 Ag). The signal was weakly positive (2.5 times the minimum threshold). At V1 and V2 (1 month after V1), HIV-1 plasma viral load (VL) was repeatedly undetectable (<40 copies/mL) using Xpert HIV-1 Viral Load (Cepheid, Sunnyvale, CA). As recommended in France, HIV Western blots (WBs) were performed. Combined HIV-1/2 WB was carried out at V1 and V2, using HIV Blot 2.2 (MP Diagnostics, Singapore) and INNO-LIA HIV 1/2 Score (Innogenetics, Gent, Belgium), respectively. In addition to HIV-1 antigens, these assays include several HIV-2 antigens (the Gag-Pol precursor for the MP test and the HIV-2 glycoproteins gp36 and gp105 for the INNO-LIA test). At V1, the combined HIV-1/2 WB was only positive for the HIV-1 p24 band, but not for the HIV-2 band corresponding to the Gag-Pol precursor. At V2, the HIV-1/2 WB profile only exhibited the HIV-1 p24 and HIV-2 gp36 bands, thus suggesting an HIV-2 primary infection.

Combined antiretroviral therapy was hence initiated 1 week after V2, with a regimen containing emtricitabine, tenofovir disoproxil fumarate, and ritonavir-boosted darunavir. Due to HIV-2 natural drug resistance to non-nucleoside reverse transcriptase inhibitors, the recommended firstline treatment options consist of 2 nucleoside reverse transcriptase inhibitors associated with a protease or integrase inhibitor. Following diagnosis, the patient also received adequate patient education sessions and psychological assistance. The patient's follow-up consisted of 4 additional visits, at 2, 3, 4, and 8 months after V1 (V3, V4, V5, and V6, respectively) (Figure 1). No white cell count anomalies were noted at V1 or over the course of the follow-up. At diagnosis (V1), his CD4 and CD8 cell counts were 1104 and 1112/mm^3, respectively, with a CD4/CD8 ratio of 0.99. Over the course of the follow-up, under antiretroviral therapy, his CD4 cell count increased by 260/mm^3 between V1 and V6, and the CD4/CD8 ratio reversed (it was 1.31 at V3 and 1.57 at V6) (Figure 1).

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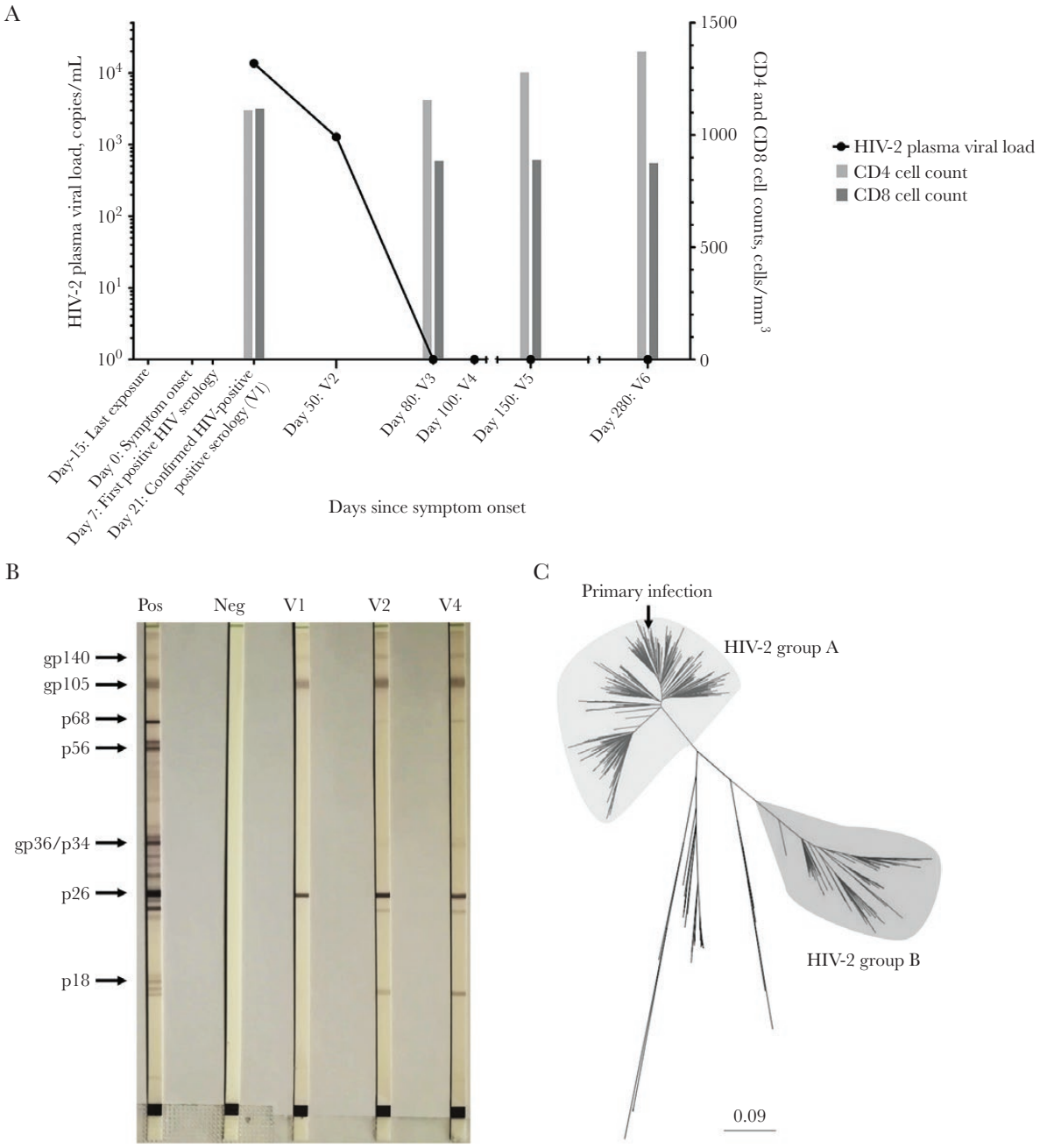

Figure 1. Changes in immunological and virological parameters during an HIV-2 primary infection. A, CD4 and CD8 cell counts and the HIV-2 plasma viral load (VL) were monitored throughout the 8-month follow-up. Antiretroviral therapy was started 1 week after V2, with a regimen containing emtricitabine, tenofovir disoproxil fumarate, and ritonavir-boosted darunavir. CD4 and CD8 cell counts are depicted as light and dark gray bars, respectively. Undetectable HIV-2 plasma VLs were assigned an arbitrary value of 1 copy/mL, and HIV-2 VLs were log-transformed and are represented as a black circle. Dates are expressed as days since symptom onset, with day –15 being the last exposure. B, HIV-2-specific Western blots were performed using New Lav Blot II (BioRad, Marne-la-Coquette, France). Longitudinal serums were tested on the same batch: Pos, positive control; Neg, negative control; V1, serum from patient at visit 1; V2, serum at visit 2 (1 month after V1); and V4, serum at visit 4 (3 months after V1). At V4, the patient was receiving antiretroviral therapy. The criteria for HIV-2 positivity are the presence of at least 1 band for each gene (Env, Gag, and Pol). Thus, the HIV-2 WB performed at V1 was indeterminate, although consistent with an HIV-2 primary infection, whereas the WB performed at V2 and V4 fulfilled the criteria for HIV-2 positivity. C, A consensus phylogenetic tree was built by maximum of likelihood method using PhyML v3.1, using a data set composed of protease and reverse transcriptase sequences obtained from the patient and from Los Alamos HIV Database, including HIV-2 groups A and B, as well as SIV viruses. Robustness of the tree was assessed by bootstrapping with 1000 replicates. The tree was edited using FigTree v1.4.3 (http://tree.bio.ed.ac.uk/software/figtree/).

Serum and plasma samples collected at V1, V2, and subsequent visits were sent to the French HIV-2 reference laboratory for specific serological and molecular assays. An HIV-2-specific WB assay (New Lav Blot II, BioRad, Marne-la-Coquette, France) was performed on samples at V1, V2, and V4 to document this suspected HIV-2 primary infection. This assay

detects antibodies directed against HIV-2 Env (gp36, gp105, and gp140), Gag (p56, p26, and p16), and Pol (p55 and p34) proteins. At V1, only weak anti-gp140, anti-gp105, anti-p26 bands and faint anti-p16 bands were present (Figure 1). This pattern is highly compatible with a recent HIV-2 seroconversion. The V2 sample (ie, before initiation of antiretroviral therapy) yielded faint anti-p68 and anti-gp36 bands. The HIV-2 WB was fully reactive to all of the antigens at V4 (3 months after V1) (Figure 1).

Plasma HIV-2 RNA quantification was performed on samples collected at V1, V2, V3, V4, V5, and V6 using a Biocentric HIV-2 RNA kit (Biocentric, Bandol, France), with a quantification threshold of 40 copies/mL. At V1, the patient had a HIV-2 plasma viral load of 13 600 copies/mL. One month later, before the antiretroviral treatment was initiated, the viremia had spontaneously decreased to 1270 copies/mL. His HIV-2 viral load was undetectable (<40 copies/mL) 1 month after treatment initiation, and it remained undetectable at subsequent visits (Figure 1).

Genotypic resistance testing was performed on samples collected at V1 and V2. HIV-2 protease, reverse transcriptase, integrase, and the V3 loop of the gp105 regions were sequenced by Sanger technology, as described by the Agence Nationale de Recherche sur le Sida et les Hépatites Virales (ANRS) [1]. Phylogenetic analyses identified this virus as belonging to HIV-2 group A, which is the main epidemic group of HIV-2. No mutations on residues associated with drug resistance were identified, and the predicted viral tropism was CCR5 [2, 3]. The protease, reverse transcriptase, integrase, and the V3 loop of gp105 region sequences were deposited in GenBank under accession numbers MG878085, MG878086, MG878087, and MG878088.

The HIV-2 cellular reservoir was estimated by quantifying HIV-2 total DNA in peripheral blood mononuclear cells (PBMCs) using a recently developed technique with a quantification threshold of 6 HIV-2 total DNA copies per polymerase chain reaction (PCR) [4]. At V4 and V5, the HIV-2 cellular reservoir was detectable, although it was below the threshold of quantification, despite the input of genomic DNA equivalent to 100 000 PBMCs.

DISCUSSION

To our knowledge, this case report describes the third case of reported primary HIV-2 infection, while it is the first case reported to have occurred after homosexual intercourse. The previous case reports of HIV-2 primary infection were only described serologically [5, 6]. Thus, the current report provides new insights into HIV-2 primary infection dynamics through serological and molecular assays, including viral load and reservoir quantification assessments.

The clinical presentation of this case of HIV-2 primary infection exhibited many similarities with HIV-1, namely upper respiratory tract symptoms, fatigue, and a transient maculopapular skin rash [7]. Analogous to HIV-1 classification, this patient was diagnosed at Fiebig stage V (RNA-positive, p24 Ag–positive, and an incomplete WB lacking the p34 band), suggesting that the infection occurred at least 3 weeks but less than 4 months prior [8]. The patient's medical and personal history suggest that the infection probably occurred during his last at-risk exposure 5 weeks before the first visit, in line with the Fiebig classification designed for HIV-1.

It has been established that the HIV-2 RNA VL is 30-fold lower than with HIV-1 in chronically infected patients [9], and this appears to be similar during primary infection. As frequently observed in HIV-2 antiretroviral-naïve patients, the HIV-2 cellular reservoir was limited in this patient [10]. Low replication of HIV-2 during the primary infection, which is a critical phase for the establishment of the HIV reservoir, may explain the low level of HIV-2 total DNA observed in this patient. Nevertheless, the early initiation of antiretroviral therapy probably also contributed to limiting the reservoir seeding, as described in HIV-1 [11]. Early initiation of antiretroviral therapy could also be responsible for the slow appearance of HIV-2-specific antibodies on WB. As in most sexually transmitted HIV infections, the transmitted virus displayed no resistance-associated mutations and it had a CCR5 tropism.

Interestingly, during the follow-up of this patient, in addition to the reversal of the CD4/CD8 ratio that is indicative of reduced lymphocyte activation in response to antiretroviral therapy, the CD4 cell count increased by 260/mm^3 in 8 months. This differs from chronically HIV-2-infected patients, for whom CD4 cell count recovery under antiretroviral drugs is often lower than expected, thus highlighting the usefulness of early treatment initiation in HIV-2 as in HIV-1 [12]. However, no extensive immunological characterization could be performed, limiting our knowledge on immunological mechanisms in this primary infection.

During HIV-1 primary infection, 40% to 90% of patients are symptomatic [7]. Diagnosis of HIV-2 primary infections may be limited by a larger proportion of asymptomatic primary infections. We hypothesize that the lower replication of HIV-2 may limit the immune response and the onset of symptoms, which may explain why only 2 HIV-2 primary infections have been reported to date.

Detecting primary HIV-2 infections can also be challenging because of technical hurdles, as HIV-2-specific testing (WB or nucleic acid testing) is not frequently available in routine settings. Although the immuno-differentiation tests recommended in the United States to confirm HIV positivity detect both HIV-2 infections and dual HIV-1/2 infections, only HIV-1-specific WB assays are performed in some countries. Due to the similarity of HIV-1 and HIV-2 capsid proteins (p24 and p26 Ag, respectively), cross-reactivity against HIV-1 p24 Ag on HIV-1-specific WB is a frequent occurrence with HIV-2-infected patients [13].

Some laboratories use HIV-1/2 combined WB, which includes an HIV-2-specific band. However, no combined HIV-1/2 WB tests detect antibodies directed against HIV-2 gp140 and gp105, which along with anti-p26 are the first anti-HIV-2 antibodies to appear. Thus, HIV-1/2 WB may lack sensitivity for HIV-2 primary infections. HIV positivity should always be confirmed with an immune differentiation test followed by specific HIV-1 and HIV-2 DNA PCR to discriminate between cross-reactivity and HIV-1/2 dual infections [14].

In conclusion, this case illustrates for the first time that during HIV-2 primary infection viral replication appears to be limited to the same extent as chronic infection. This patient had a moderate level of viral reservoir in PBMCs, which was probably at least partly due to early initiation of antiretroviral therapy. This also emphasizes the importance of discriminating between HIV-1 and HIV-2 for all new HIV infections, regardless of the patient's risk factors, age, and origin. HIV-2 should be kept in mind as a possibility when screening all patients at risk of HIV and other sexually transmitted infections.

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