Adult T-Cell Leukemia/Lymphoma in a Caucasian Patient After Sexual Transmission of Human T-Cell Lymphotropic Virus Type 1

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Adult T-cell leukemia/lymphoma (ATLL), a T-cell neoplasm caused by human T-cell lymphotropic virus type 1 (HTLV-1), develops in the majority of cases in individuals who were infected with HTLV-1 as young children, by their mother during prolonged breastfeeding. We report the case of a Caucasian French man, whose parents were HTLV-1-seronegative and who developed ATLL after HTLV-1 sexual transmission by a Cameroonian woman. This hypothesis was corroborated by genotyping of the patient's virus, which revealed an HTLV-1B strain, found only in Central Africa, especially in Cameroon. Thus, ATLL may develop after HTLV-1 infection during adulthood, outside breastfeeding.

Keywords. ATLL; HTLV-1; HTLV-1 transmission; lymphoma; viral genotyping.

Received 25 November 2014; accepted 2 March 2015.

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Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofv032

Adult T-cell leukemia/lymphoma (ATLL) is an aggressive T-cell lymphoproliferation caused by human T-cell lymphotropic virus type 1 (HTLV-1) [1, 2]. This oncogenic human retrovirus can be acquired by mother-to-child transmission through prolonged breastfeeding, sexual transmission, or from transfused infected blood cells or intravenous (IV) drug abuse [2]. Human T-cell lymphotropic virus type 1 infects at least 5–10 million individuals worldwide and, among them, 1%–5% will develop ATLL during their lifetime [3]. The results of several studies showed that most cases of ATLL develop in individuals who have been infected with HTLV-1 as young children via their mothers' breast milk [4–7]. The very rare ATLL cases observed after transfusion or sexual transmission are still being debated [8–11]. In this study, we report on a Caucasian French patient, with HTLV-1-seronegative parents, who developed ATLL 18 years after highly probable sexual transmission of HTLV-1 through repeated unprotected sexual intercourse with a Cameroonian woman. Indeed, genotyping of the patient's virus revealed infection with an HTLV-1 subtype-B strain, typically of Central African origin, especially Cameroon. This case definitively confirms the hypothesis that ATLL can develop, albeit rarely, after infection during adulthood, outside breastfeeding.

CASE REPORT

The patient's written consent was obtained for this report. A 43-year-old Caucasian French man was referred to our hospital in 2002 for cutaneous T-cell lymphoma (CTCL) associated with positive HTLV-1 serology. The patient had no remarkable personal or family medical history. He was born and raised in Mainland France, had no siblings, and was exclusively fed with bottle milk during childhood. His current history had begun 8 years earlier (1994) with the development of erythematosquamous plaques on his ankles, with ascending evolution over the next 5 years and progressive involvement of legs, buttocks, lumbar region, and axillary areas, affecting nearly 30% of his body surface. Topical corticosteroids were applied initially without formal diagnosis, with an initial response followed by relapse. In 2001, 3 cutaneous nodular lesions (20–30 mm) appeared at different sites (thigh, eyebrow, and leg), with necrotizing evolution and atrophic scaring. Physical examination revealed no lymphadenopathy or hepatosplenomegaly.

A nodule was biopsed: a band-like mononuclear cell infiltrate was seen in the upper dermis with markedly epidermotropic large cells with indented nuclei (Figure 1A–C). Immunolabeling revealed the infiltrate to be mainly constituted by

$CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, and $CD25^+$ T cell, but not CD7 and CD8. Molecular analysis showed clonal T-cell receptor (TCR)-γ and β-gene rearrangements. Human T-cell lymphotropic virus type 1 serology was positive by both immunofluorescence on MT2 cells and particle-agglutination (PA) assays (Serodia HTLV-1; Fujirebio Inc, Tokyo, Japan) and then confirmed by Western blotting (HTLV Blot 2.4; MP Biomedicals Asia Pacific Pte. Ltd, Singapore), with typical complete seroreactivity (p19, p24, pr53, GD21, and MTA-1). Anti-HTLV-1 antibody titers, determined by serial dilution, were 1/10 240 on MT2 cells and 1/2048 in the PA assay. A circulating HTLV-1 provirus load determined by quantitative polymerase chain reaction (PCR) was relatively high: 18.6 copies/100 peripheral blood mononuclear cells (PBMCs). Complete blood count, especially lymphocyte count, was normal; serum lactate dehydrogenase and calcemia levels were within their normal ranges. The blood smear showed 5% flower cells (Figure 1D). Flow cytometric immunophenotyping of circulating lymphocytes detected 8% $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, $CD7^-$, $CD25^+$, and $HLADR^+$ cells. T-cell clonality was demonstrated by the presence of a TCR-γ gene rearrangement detectable by PCR analysis of blood cells. This TCR-γ gene rearrangement was the same as that found in the skin. Moreover, analysis of the HTLV-1 integration sites using inverse PCR demonstrated HTLV-1 clonal population in PBMC DNA with identical clones over time [12]. Bone marrow aspiration and trephine biopsy revealed no malignant involvement. Human immunodeficiency virus serology was negative, serum protein electrophoresis and immunoglobulins levels were normal, and antinuclear antibodies were absent. There was no argument for an underlying immunocompromised status. Thoracic, abdominal, and pelvic computed-tomography scans showed no lymph node, liver, or spleen enlargement, but it found multiple micronodular lesions in the lungs. Therefore, according to the Shimoyama classification, smouldering ATLL was diagnosed [1].

Treatment consisted of PUVA therapy followed by zidovudine and interferon-alpha [13, 14]. Complete remission was rapidly obtained. Zidovudine was discontinued in 2008 after 6 years of treatment due to persistent neutropenia and elevated liver enzymes. Absolute neutrophil count and liver enzymes subsequently normalized. At the last follow-up visit (2014), the patient continued interferon-alpha and was in sustained

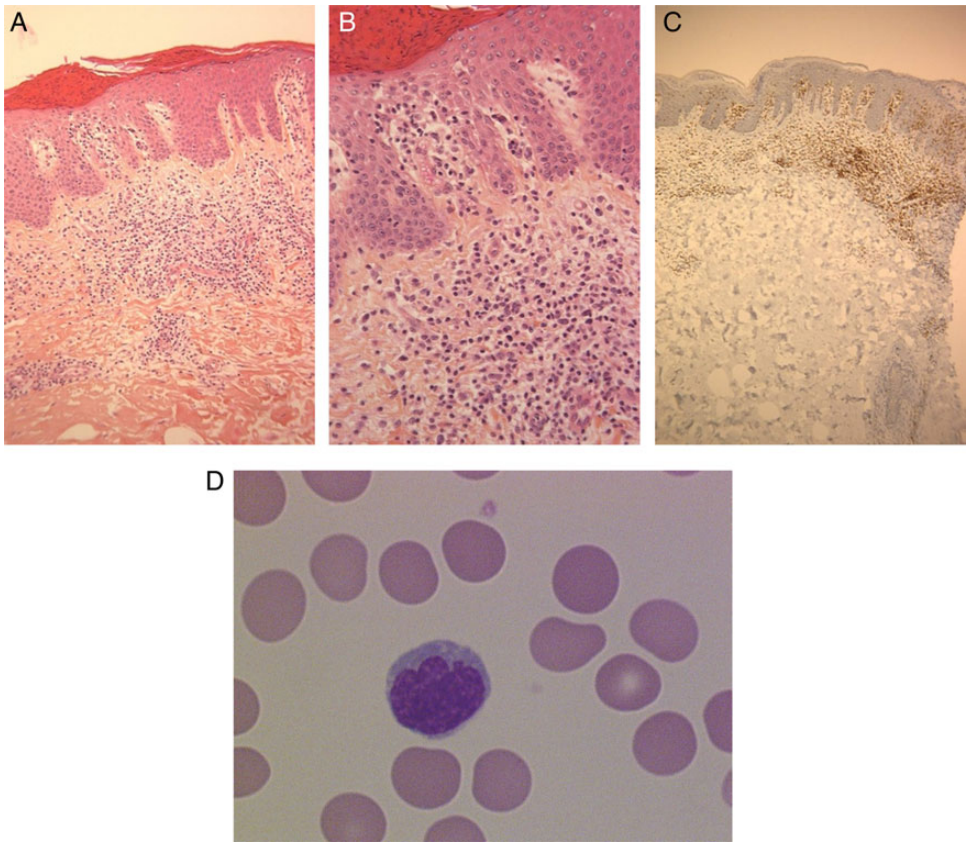

Figure 1. (A) Biopsy of a skin nodule showing parakeratosis surrounding acanthotic epidermis, with a band-like mononuclear cell infiltrate tending to gain the epidermis, and (B) marked epidermotropism of large lymphocytes with hyperchromatic nuclei (A and B: hematoxylin and eosin, A × 100; B × 200). C, The band-like epidermotropic infiltrate was strongly labeled with anti-CD3 antibody (×50). D, Blood smear morphology: atypical medium size lymphocyte with agranular and weakly basophilic cytoplasm, condensed chromatin, and convoluted nucleus, designated a "flower cell" (May-Grünwald Giemsa, ×1000).

complete remission. Blood analysis showed no TCR-γ gene rearrangement.

Because both of his parents were Caucasian and HTLV-1-seronegative (Abbott HTLV-I/HTLV-II EIA, Abbott Park, Illinois), and the patient had no known risk factor for HTLV-1 exposure through blood products or IV drug abuse, we wondered about the route of infection. Sexual transmission of HTLV-1 was considered the most likely, because the patient had lived for 8 months with a Cameroonian woman with whom he had repeated unprotected sexual intercourse during a prolonged stay in Cameroon when he was 17 years old. The hypothesis of sexual transmission was corroborated by the genotyping of the virus isolated from the patient. Indeed, sequencing of a 758-base pair DNA fragment of the long terminal repeat region extracted from 2 PBMCs samples (PH1512 and PH1515) collected at a 7-year interval demonstrated that the virus infecting this patient belonged to the Central African subtype B (Figure 2). Pertinently, these HTLV-1 provirus strains clustered (bootstrap value, 84) with 2 strains (PH236 and T49) previously characterized in individuals of Cameroonian origin.

DISCUSSION

This patient originally consulted for a CTCL characterized by a clonal skin proliferation of $CD4^+$ and $CD25^+$ cells, associated with small percentages of those cells circulating in his blood. Human T-cell lymphotropic virus type 1 infection was demonstrated based on the strong specific seropositivity confirmed by Western blotting and detection of the HTLV-1 genome in the blood. Inverse PCR also identified an HTLV-1 clonal population in his blood. Taken together, those findings clearly demonstrated that our patient suffered from smouldering ATLL. Adult T-cell leukemia/lymphoma is a mature T-cell malignancy observed mainly in patients from high HTLV-1-endemic

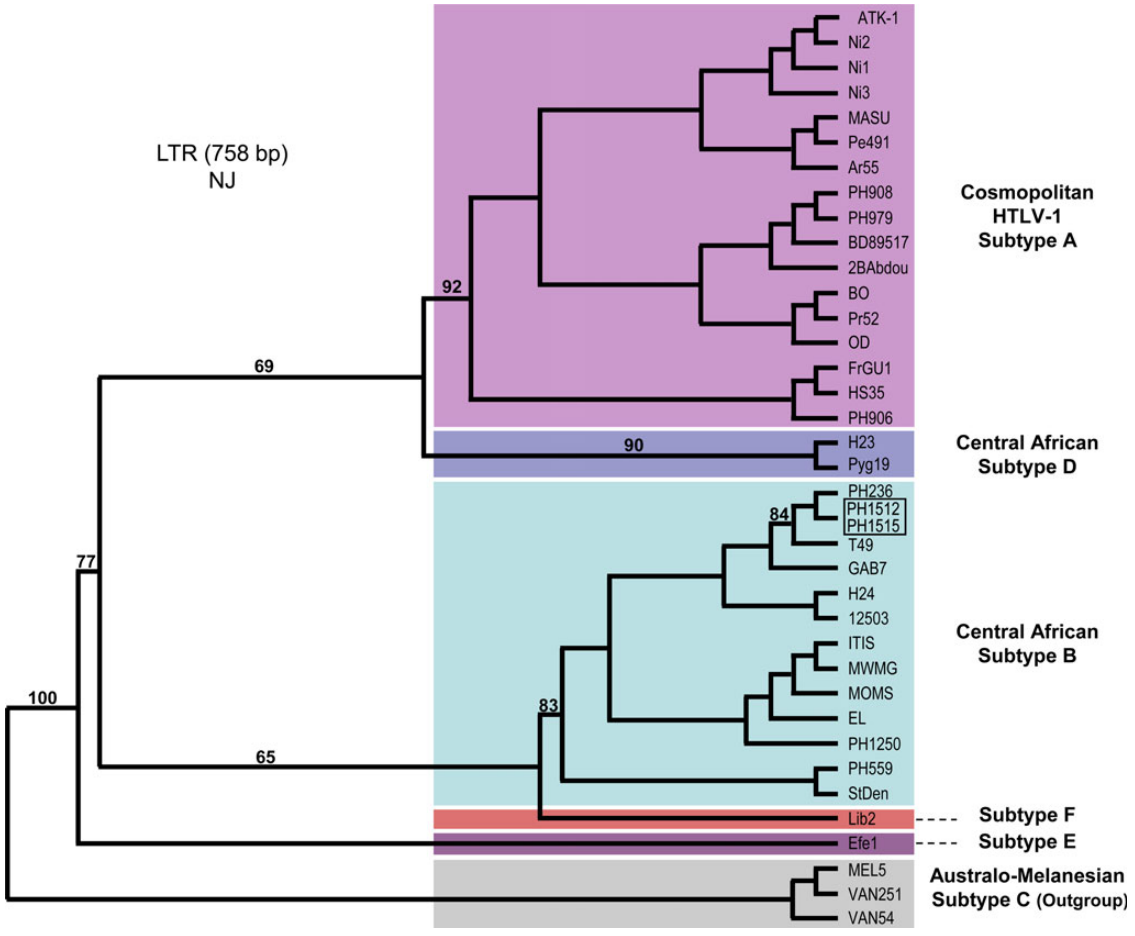

Figure 2. Phylogenetic tree generated using the neighbor-joining (NJ) method on a 758-base pair (bp) fragment of the long terminal repeat (LTR) region for available sequences of 38 human T-cell lymphotropic viruses type 1 (HTLV-1), including the 2 sequences generated in this study (boxed in bold type). The HTLV-1 strains were aligned with the DAMBE program (version 4.2.13). The final alignment was subjected to the Model-test program (version 3.6) to select, according to the Akaike information criterion, the best model to apply to phylogenetic analyses. The selected model was the General Time Reversible model. Bootstrap values were calculated for 1000 replicates, and those values at some tree nodes indicate occurrence frequencies for 100 trees. Subtypes A–D are the 4 major HTLV-1 subtypes. Subtype B corresponds to the Central African subtype including the PH1512 and PH1515 sequences generated herein.

regions, eg, southwestern Japan, the Caribbean basin and South America, sub-Saharan Africa, and localized areas of Iran and Australo-Melanesia. Among HTLV-1-infected individuals worldwide, only 1%–5% will develop ATLL during their lifetimes, after a prolonged latency period (20–60 years), during which sustained oligoclonal or polyclonal expansion of infected T cells occurs, associated with a high level of genetic instability. At the molecular level, HTLV-1 oncogenicity mainly depends on the virus-encoded Tax oncoprotein. By interfering with genome repair, cell cycle, and apoptosis machinery, Tax plays key roles in inducing clonal expansion and genetic instability of infected cells, leading to early leukemogenesis. Recently, it was shown that HTLV-1 bZIP factor, encoded by the minus strand of the HTLV-1 provirus and constitutively detectable in ATLL, could play a significant role in leukemogenesis and the maintenance of leukemic clones [15]. Given its long latency period, infection early in life is considered the main risk factor for ATLL, although some cofactors, eg, coinfection with *Strongyloides stercoralis* [2] or an immunocompromised status, might also be involved [9, 16–18]. Thus, in contrast to what is observed in tropical spastic paraparesis/HTLV-1-associated myelopathy, ATLL seems to develop only after mother-to-child transmission, and ATLL occurrence after sexual or blood transmission remains highly controversial.

Molecular epidemiologic studies on HTLV-1 demonstrated that, despite being a retrovirus, this oncogenic agent exhibits marked genetic stability [19]. That property is very probably linked to replication through clonal expansion of infected cells, rather than using the error-prone reverse transcriptase. Seven molecular genotypes linked to the geographic or ethnic origin of the infected individual have been reported. They include the subtype A, also known as the cosmopolitan subtype, which includes the prototype HTLV-1 sequence from Japan and is found in many HTLV-1-endemic areas worldwide. The other subtypes B, D, E, F, and G are found only in Central Africa, and the subtype C is only found in Australo-Melanesia [3, 20]. The very low genetic HTLV-1 drift in vivo associated with such genotype geographic specificity can be used as a molecular means to better understand ancient movements of infected populations but also to monitor virus transmission and trace the origin of a virus in a given individual [19, 20]. The vast majority of ATLL cases seen in Europe occur in patients of black ancestry from the West Indies or West Africa. In almost all of those patients, the cosmopolitan subtype-A viral genotype is found.

Our main question was as follows: How did this Caucasian patient with HTLV-1-seronegative parents acquire HTLV-1 infection? The absence of blood transmission and the fact that the patient had sexual intercourse over several months in Cameroon (a high HTLV-1-endemic area) strongly suggested that the virus had been sexually acquired. Therefore, we performed virus genotyping to strengthen this hypothesis. We found that the patient was infected with a typical HTLV-1 strain of the subtype B, a rare genotype, absent in Europe, and found only in Central Africa, especially Cameroon.

CONCLUSIONS

This case demonstrates the occurrence of ATLL in a Caucasian patient infected with an HTLV-1 subtype-B strain, found only in Central Africa, and definitively confirms the hypothesis that ATLL can develop after infection during adulthood, outside breastfeeding, and especially after sexual transmission of HTLV-1.

Acknowledgments

We thank Janet Jacobson for editorial assistance.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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