Immune Compromise in HIV-1/HTLV-1 Coinfection With Paradoxical Resolution of CD4 Lymphocytosis During Antiretroviral Therapy

A Case Report

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Abstract: Human immunodeficiency virus type-1 (HIV-1) and human T lymphotropic virus type-1 (HTLV-1) infections have complex effects on adaptive immunity, with specific tropism for, but contrasting effects on, CD4 T lymphocytes: depletion with HIV-1, proliferation with HTLV-1. Impaired T lymphocyte function occurs early in HIV-1 infection but opportunistic infections (OIs) rarely occur in the absence of CD4 lymphopenia. In the unusual case where a HIV-1 infected individual with a high CD4 count presents with recurrent OIs, a clinician is faced with the possibility of a second underlying comorbidity.

We present a case of pseudo-adult T cell leukemia/lymphoma (ATLL) in HIV-1/HTLV-1 coinfection where the individual fulfilled Shimoyama criteria for chronic ATLL and had pulmonary Mycobacterium kansasii, despite a high CD4 lymphocyte count. However, there was no evidence of clonal T-cell proliferation by T-cell receptor gene rearrangement studies nor of monoclonal HTLV-1 integration by high-throughput sequencing. Mutually beneficial interplay between HIV-1 and HTLV-1, maintaining high level HIV-1 and HTLV-1 viremia and proliferation of poorly functional CD4 cells despite chronicity of infection is a postulated mechanism.

Despite good microbiological response to antimycobacterial therapy, the patient remained systemically unwell with refractory anemia. Subsequent initiation of combined antiretroviral therapy led to paradoxical resolution of CD4 T lymphocytosis as well as HIV-1 viral suppression and decreased HTLV-1 proviral load. This is proposed to be the result of attenuation of immune activation post-HIV virological control.

This case illustrates the importance of screening for HTLV-1 in HIV-1 patients with appropriate clinical presentation and epidemiological risk factors and explores mechanisms for the complex interactions on HIV-1/HTLV-1 adaptive immunity.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, ATLL = adult T cell leukemia/lymphoma, BAL = bronchoalveolar lavage, cART = combination antiretroviral therapy, CSF = cerebrospinal fluid, DNA = deoxyribonucleic acid, HAM = HTLV-1 associated myelopathy, Hb = hemoglobin, HIV-1 = human immunodeficiency virus type-1, HPLC = high performance liquid chromatography, HTLV-1 = human T lymphotropic virus type-1, NR = normal range, OI = opportunistic infection, PBMCs = peripheral blood mononuclear cells, PVL = proviral load, STLV = simian T-lymphotropic virus, TCR = T cell receptor, UIS = unique integration site, VL = viral load.

INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1) is well known to cause opportunistic infection (OI) and this is typically accompanied by declining levels of CD4 T-lymphocytes leading to impaired cell-mediated immunity. In the unusual case where a HIV-1 infected individual with a high CD4 cell count presents with recurrent infections, a clinician is faced with the possibility of a second underlying comorbidity. Coinfection with a second retrovirus, human T lymphotropic virus type-1 (HTLV-1), should also be considered, particularly in individuals of specific ethnic or geographic origins with a prevalence of greater than 1% in the general population. HIV-1 and HTLV-1 infections have complex effects on adaptive immunity, with specific tropism for, but contrasting effects on CD4+ T-cells.

An estimated 10 to 20 million people worldwide are infected with HTLV-1 with prevalence exceeding 1% in southern Japan, central Africa, and the Caribbean.1 HTLV-1 infection is associated with asymptomatic carriage in more than 90% of infections. HTLV-1 associated myelopathy (HAM) occurs in 0.3% to 3% of carriers and the lifetime risk of adult T cell leukemia/lymphoma (ATLL) is 1% to 5%.2,3 HTLV-1 is also associated with a range of inflammatory diseases: HAM,
uveitis, pneumonitis, lymphocytic arthritis, and bronchiectasis. HTLV-1 infection is also associated with a range of infections implying selective immune impairment, most notably disseminated strongyloidiasis infection, Norwegian scabies, infective dermatitis, bladder, and kidney infections.1,2

Rhee et al’s review of the literature showed that being a carrier for HTLV-1 was a risk factor for OI, particularly in geographical areas with high HTLV-1 prevalence.4–7 Case–control studies carried out in geographical areas with high HTLV-1 prevalence showed an increased risk of tuberculosis (MTB) coinfection in case–control studies.

A patient with HIV-1/HTLV-1 coinfection presenting with an acquired immunodeficiency syndrome (AIDS) defining diagnosis of Mycobacterium kansasii and pseudo-adult T-cell leukemia/lymphoma (ATLL) is presented. The mechanism of potentiated immune activation driving proliferation is postulated. Informed consent was obtained from the patient before all investigations and before publication of this case report.

CASE

The patient, a 47-year-old West Indian man was diagnosed with HIV-1 infection in the United Kingdom in 2002. He was heterosexual, had no history of injecting drug use and had a 20 pack year smoking history. He originally presented with recurrent cutaneous fungal infections, bacterial tonsillitis, varicella zoster infection, and oral candida. At diagnosis, his CD4 lymphocyte count was 757 cells/mm³ (normal range [NR] 300–1400) and HIV-1 viral load (VL) was 26,905 copies/ml.

He remained clinically stable without antiretroviral therapy until 2010 when he presented with symptomatic anemia, night sweats, and a productive cough unresponsive to antimycobacterial therapy (rifampicin, isoniazid, ethambutol), he remained symptomatic with weight loss, productive cough, and refractory anemia requiring multiple transfusions. HIV-1 VL was now 7.44 × 10⁶ copies/ml, CD4⁺ count 2477 cells/mm³. At this point HTLV-1 infection was considered and anti-HTLV-antibodies were detected with Western blot confirmation. HTLV-1 proviral load (PVL) was 42.9 deoxyribonucleic acid (DNA) copies/10⁶ peripheral blood mononuclear cells (PBMCs). Ninety-two percent of CD4⁺ lymphocytes expressed CD25 (NR 15.7–34.9) with no evidence of clonal T cell receptor (TCR) gene rearrangement.

Combination antiretroviral therapy (cART) was commenced in August 2011 with emtricitabine, etravirine, and darunavir/ritonavir (a tenofovir sparing regimen was selected in light of his renal function). Within 3 months, he showed clinical and radiological improvement. The CD4⁺ count decreased to 1495/mm³ HTLV-1 PVL to 20.4% and HIV VL to 5098 copies/ml. Cerebrospinal fluid (CSF) obtained 4 months post initiation of cART revealed 538 copies/ml CSF (ppaired plasma HIV VL 932 copies/ml) and CSF HTLV-1 PVL of 41.8 % CSF white cells (paired PBMC PVL 28.2 %). After nine months on cART, HIV VL was undetectable in plasma, with decreases in HTLV-1 PVL to 10.7% PBMCs and CD25 biochemical profile were unremarkable. Urinalysis revealed microscopic hematuria and proteinuria with a urine protein-creatinine ratio of 146 (normal range <20). His estimated glomerular filtration rate was 79 ml/minute/1.73 m² (NR 59 ml/minute/1.73 m²) and computerized tomography of kidneys, ureters and bladder, flexible cystoscopy, renal, and prostate ultrasound were unremarkable. Computerized tomography of the thorax revealed bilateral upper lobe bronchiectasis along with several ill-defined nodules, some with cavitation, and foci of consolidation in both the upper lobes, significant right middle lobe consolidation and associated volume loss (Figure 1). Bronchoalveolar lavage (BAL) washings revealed an acute inflammatory response with no malignant cells. M. kansasii grew from BAL and sputum culture. HIV-1 VL at this time was 4.62 × 10⁶ copies/ml, absolute lymphocyte count 8000 cells/mm³ (NR 1100–3600) and CD4⁺ count 2239 cells/mm³.

Despite sputum culture conversion within 6 months of antmycobacterial therapy (rifampicin, isoniazid, ethambutol), he remained symptomatic with weight loss, productive cough, and refractory anemia requiring multiple transfusions. HIV-1 VL was now 7.44 × 10⁶ copies/ml, CD4⁺ count 2477 cells/mm³. At this point HTLV-1 infection was considered and anti-HTLV-antibodies were detected with Western blot confirmation. HTLV-1 proviral load (PVL) was 42.9 deoxyribonucleic acid (DNA) copies/10⁶ peripheral blood mononuclear cells (PBMCs).

Salient laboratory findings were: erythrocyte sedimentation rate of 126 mm/hour (NR 0–10 mm/hour), hemoglobin (Hb) 7 g/dl (NR 12.5–17.0), mean cell volume 76.8 fl (NR 83.0–101.0), ferritin 410 μg/L (NR 20–300), high performance liquid chromatography (HPLC) showed HbA 4.6% (NR 2.0–3.3%); HbA 2.3% (NR 0–1%), Blood film showed anisopoikilocytosis, mature lymphocytosis with 14% atypical lymphocytes and no flower cells. Serum B12: 360 ng/L (NR 160–800), red cell folate: 145.6 ng/ml (NR 126–480), iron: 23 μmol/L (NR 9–29), Total iron binding capacity: 31 μmol/L (NR 49–78), transferrin saturation: 74 (NR 20–45%), pretransfusion reticulocyte count was 48.9 × 10⁹ (NR 28.1–86.1 × 10⁹), reticulocyte %: 1.6 (0.52–1.84%). A vasculitic screen was negative for anticyclic citrullinated peptide, antineutrophil cytoplasmic antibody, antinuclear antibody, and antiglomerular basement antibody. Serology revealed no evidence of previous or current hepatitis B or C virus infection. There was no evidence of hematological malignancy, Epstein–Barr virus, parvovirus or human herpes virus-8 infection on bone marrow examination. Upper and lower gastrointestinal endoscopy revealed only chronic gastritis. Serum albumin was 24 g/L (NR 22–47) and liver transaminases and bone

![FIGURE 1. CT thorax at the time of diagnosis of M. kansasii showing consolidation and bronchiectasis in upper lobes bilaterally.](Image)
expression on CD4\(^+\) cells to 87%. Table 1 summarizes total lymphocyte, CD4 lymphocyte count, HIV-1 and HTLV-1 VL before and in response to cART.

At HTLV-1 diagnosis, HTLV-1 unique integration site (UIS) analysis by Illumina high-throughput sequencing\(^9\) revealed a polyclonal distribution in which the largest clone contributed 1.77% of the total HTLV-1 PVL. One year later, HTLV-1 PVL 19%, the polyclonal distribution was similar and the same clone remained largest, contributing 0.96% of the total HTLV-1 PVL (Figure 2).

At HTLV-1 diagnosis, the majority of CD4\(^+\) T cells, as determined by flow cytometry, were effector memory cells (TEM, CD45RA\(^+\)CD127\(^-\)CD25\(^-\)FOXP3\(^-\)) immunophenotype. One year later, there was reduction in both absolute and relative frequency of CD4 TEM cells but no change in immunophenotype.

He remains well 4 years later.

**DISCUSSION**

This case caused diagnostic uncertainty since the absolute lymphocyte count, HTLV-1 serology and % atypical lymphocytes fulfilled Shimoyama criteria\(^{10}\) for the diagnosis of chronic ATL. However, there was no evidence of clonal T-cell proliferation by TCR gene rearrangement studies nor of monoclonal HTLV-1 integration by high-throughput sequencing.

HTLV-1 infection results in increased T lymphocyte proliferation, which is usually balanced by a higher rate of infected cell death due to immune surveillance.\(^2\) Total lymphocyte, CD4 and CD8 T lymphocyte subsets are usually within the normal range in HTLV-1 mono-infection. Unlike HIV-1 infection in which viromia is maintained by infectious spread, HTLV-1 PVL, in chronic infection is thought to be substantially maintained by proliferation of infected cells and HTLV-1 integration site analysis reveals multiple clonal expansions of CD4 T lymphocytes.\(^3\) The very high HIV-1 viromia, despite the chronicity of infection, may reflect the abnormally high CD4 cell count due to HTLV-1 infection, similar to that seen in infants and young children. This patient had lymphocytosis predominantly due to an increased frequency of activated CD4\(^+\)CCR4\(^+\)TEM cells. A high proportion of HTLV-1-infected cells express CCR4. It has been suggested that active HIV infection increases CCR4\(^+\) T-cells via secretion of the CCR4 ligands TARC and MDC by activated monocyte/macrophages.\(^1\) This would result in the proliferation of HTLV-1-infected CCR4\(^+\) T cells. We postulate that the coinfection with the 2 viruses led to overproduction of poorly functional lymphocytes whilst providing an environment for high levels of HIV virion production. It is possible that CD4\(^+\) T-lymphocytes were coinfected with the 2 viruses, but we have not been able to demonstrate this.

If, despite the high CD4 cell count, HIV-1 was contributing to high CD4 lymphocyte turnover, treatment of HIV-1 with cART might be expected to further increase the CD4 cell count, unmasking the true degree of HTLV-1-related T lymphocyte proliferation. Data from Beilke et al\(^{12}\) suggest that where individuals with HIV-HTLV-1 coinfection have high HTLV-1 VL, cART has limited efficacy in controlling HTLV-1 viremia. However, in this subject cART, which was HIV-1 specific, was associated with normalization of CD4\(^+\) counts and a significant decrease in the proportion of PBMCs infected with HTLV-1. Whilst zidovudine with lamivudine has not impacted on HTLV-1 VL in patients with HAM,\(^{13}\) zidovudine in combination with interferon-\(\alpha\) has improved the outcome in ATL.\(^{14}\) Raltegravir has been shown to prevent HTLV-1 infection in vitro.\(^{15}\) In baboons infected with simian (S) TLV-1, treatment with sodium valproate, combined with zidovudine, resulted in significant, sustained reduction in STLV-1 VL.\(^{16}\) Raltegravir may be a suitable alternative, since the role of ART combined with histone deacetylase inhibition is to prevent an initial increase in HTLV-1 viral replication associated with increased HTLV-1 transcription. The anti-HTLV-1 efficacy of zidovudine, raltegravir, and histone deacetylase inhibitors requires further clinical evaluation and may only impact on continuing infectious spread.\(^{13–16}\) The normalization of the CD4\(^+\) cell count, with a paradoxical decrease in CD4\(^+\) count during HIV-specific cART, suggested proliferation of HTLV-1-

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**TABLE 1.** Total Lymphocyte, CD4 Lymphocyte Count, Human Immunodeficiency Virus-1 and Human T-Lymphotrophic Virus Type-1 Viral Load Before and in Response to Combination Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Time Point</th>
<th>June 2003</th>
<th>November 2010</th>
<th>August 2011</th>
<th>November 2011</th>
<th>April 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of clinical management</td>
<td>Time of diagnosis of HIV-1</td>
<td>Pre-commencement of M. kansasii treatment</td>
<td>Month 6 of M. kansasii treatment/pre-commencement of cART</td>
<td>3 months after commencement of cART</td>
<td>9 months after commencement of cART</td>
</tr>
<tr>
<td>Total lymphocyte count (cells/mm(^3)) (NR 1100–3600)</td>
<td>6197</td>
<td>8000</td>
<td>5900</td>
<td>4600</td>
<td>2600</td>
</tr>
<tr>
<td>CD4 lymphocyte count (cells/mm(^3)) (NR 300–1400)</td>
<td>757</td>
<td>2239</td>
<td>2477</td>
<td>1495</td>
<td>939</td>
</tr>
<tr>
<td>HIV-1 viral load (copies/ml)</td>
<td>26,905</td>
<td>4.62 (\times) 10(^6)</td>
<td>7.44 (\times) 10(^6)</td>
<td>5098</td>
<td>&lt;40</td>
</tr>
<tr>
<td>HTLV-1 proviral load (DNA copies/100 PBMC)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>42.9</td>
<td>20.4</td>
<td>10.7</td>
</tr>
</tbody>
</table>

\(\text{cART} = \text{combination antiretroviral therapy; DNA} = \text{deoxyribonucleic acid; HIV-1} = \text{human immunodeficiency virus-1; HTLV-1} = \text{human T-lymphotrophic virus type-1; PBMC} = \text{peripheral blood mononuclear cells.}\)
infected CD4 T-cells driven by HIV-related immune activation; this interpretation was supported by the observation of polyclonal HTLV-1 integration at both time points.

In conclusion, we present a case of pseudo-ATLL in a HIV-1 infected individual whose high CD4 counts were deceptive as he was significantly immunosuppressed. His high CD4 count and ethnic origin prompted screening for HTLV-1 coinfection. Paradoxically, there was a significant improvement of CD4 lymphocytosis and HTLV-1 VL post commencement of HIV-1 specific cART. We postulate that mutually beneficial interplay between HIV-1 and HTLV-1 maintained high loads of each virus, and proliferation of poorly functional CD4⁺ cells despite chronic infection. We suggest that the likely mechanism was immune activation of T-cells, which was attenuated by HIV-1 virological control with cART.

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REFERENCES


