Progressive HIV infection in the presence of a raised CD4\(^+\) count: HIV/HTLV-1 co-infection

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There are a number of pathophysiological causes for a normal or raised CD4 count in the context of progressive HIV infection. These include various co-infections, previous splenectomy, and lymphoproliferative disorders. Such circumstances can both confound HIV diagnosis and delay initiation of chemoprophylaxis and highly active antiretroviral therapy (HAART). We describe the case of a patient co-infected with HIV and human T-cell lymphotropic virus type 1 (HTLV-1) who, prior to HAART initiation, was found to have progressive immune deficiency associated with a raised CD4 count.

A 51-year-old married man from Gauteng province, South Africa (SA), originally from the Northern Cape, tested HIV-positive on an enzyme-linked immunosorbent assay (ELISA) in March 2002 as part of a routine medical examination for insurance purposes. His CD4 count was 794 cells/\(\mu\)l and his HIV viral load was 19,365 copies/ml. He gave no history of any infectious diseases, but was receiving treatment for hypertension. On examination he was generally healthy, with normal vital signs and all systems proved unremarkable. On account of being asymptomatic with a CD4 count within normal range, he was neither initiated on highly active antiretroviral therapy (HAART) nor chemoprophylaxis, and was told to follow-up with his general practitioner for regular immune monitoring (Table 1).

An abnormally high CD4 count was detected on follow-up in September 2002 prompting T-cell receptor polymerase chain reaction (PCR) studies, which revealed no
CASE REPORT

HTLV-1 was the first retrovirus to be identified in humans and is structurally related to other viruses within the retroviridae family, such as HIV-1 and HIV-2, sharing similar routes of transmission. Since its discovery in 1979 three additional human deltaretroviruses (HTLV-2, HTLV-3 and HTLV-4) have been found, but only HTLV-1 and HTLV-2 have so far been associated with human disease. Antibodies to HTLV-1 were first identified in SA in 1984 and the first report of isolation of the virus was published in 1988. Subsequently, a number of seroprevalence studies have been conducted in SA, where HTLV-1 has been found to be endemic in areas of Mpumalanga, the Eastern Cape, Free State and KwaZulu-Natal (KZN). However, there are no recent representative data regarding prevalence in the general SA population or specific patient subgroups.

Like other human retroviruses, HTLV-1 causes a lifelong infection of T-lymphocytes, in particular CD4+ cells. However, unlike HIV, the immunological hallmark of HTLV-1-infected individuals is a CD4+ count, it was felt that the patient would benefit from ART on account of being clinically immune-compromised and having a high HIV viral load. He was initiated on a regimen of Truvada (tenofovir/emtricitabine) and efavirenz (EFV) to which he responded well with a drop in RNA copies/ml of >2 log10 after three months of treatment and an undetectable HIV viral load six months thereafter. As the CD4+ count remained above normal limits, repeat bone marrow and flow cytometry studies were carried out, identifying a population of T-lymphocytes with abnormal flow characteristics. T-cell receptor PCR showed the presence of a clonal cell population and bone marrow histology revealed infiltration by tumour cells with scattered atypical uninucleated cells and binucleated Reed-Sternberg cells. Immunophenotypic analysis showed no overt evidence of a B-cell lymphoproliferative disorder. Antibodies to human T-cell lymphotropic virus type 1/2 (HTLV-1/2) were detected by ELISA and the patient was diagnosed with a smouldering type of adult T-cell leukaemia/lymphoma (ATLL) secondary to HTLV-1 infection (HTLV-2 not being associated with this condition). He was treated with four cycles of infusional chemotherapy consisting of etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (EPOCH), which he tolerated well. Interferon-alpha therapy was subsequently commenced and maintained three times per week. At the time of writing, the patient is clinically well with no neurological deficits, an undetectable HIV viral load and a CD4+ count of 4 430 cells/μl.

Discussion

HTLV-1 was the first retrovirus to be identified in humans and is structurally related to other viruses within the retroviridae family, such as HIV-1 and HIV-2, sharing similar routes of transmission. Since its discovery in 1979 three additional human deltaretroviruses (HTLV-2, HTLV-3 and HTLV-4) have been found, but only HTLV-1 and HTLV-2 have so far been associated with human disease. Antibodies to HTLV-1 were first identified in SA in 1984 and the first report of isolation of the virus was published in 1988. Subsequently, a number of seroprevalence studies have been conducted in SA, where HTLV-1 has been found to be endemic in areas of Mpumalanga, the Eastern Cape, Free State and KwaZulu-Natal (KZN). However, there are no recent representative data regarding prevalence in the general SA population or specific patient subgroups.

Like other human retroviruses, HTLV-1 causes a lifelong infection of T-lymphocytes, in particular CD4+ cells. However, unlike HIV, the immunological hallmark of HTLV-1-infected individuals is a sustained proliferation of T-cells driven by the HTLV-1-encoded Tax protein. The subsequent transactivation of cellular genes by the Tax-encoded region can result in malignant transformation, although this is rare. In the majority of cases, cytotoxic T-cells effectively control the virus by lysis of infected lymphocytes, which in turn results in the release of inflammatory cytokines that can be pathogenic. On account of these various pathophysiological mechanisms, HTLV-1 is associated with a diverse range of pathology, including malignant disease, inflammatory syndromes and infective complications. A number of these conditions have been described in SA, including ATLL, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infectious dermatitis. Although the life-time risk for HTLV-1-associated diseases in general is considered close to 10%, an indication of a long history of viral-human co-evolution, this may be an under-representation when the interaction between HTLV-1 and other infective agents is considered. TB has been found to occur more frequently in patients infected with HTLV-1 and is also thought to be associated with a worse prognosis. HTLV-1 has been shown to up-regulate hepatitis C viral replication and is implicated as a co-factor in the development of hepatocellular carcinoma. Furthermore, two studies have demonstrated an increased rate of cervical carcinoma in HTLV-1-infected patients. Whether HIV-1 co-infection with HTLV-1 is associated with a faster progression to AIDS remains a contentious issue, although a number of studies have suggested as much. What is, however, less controversial and perhaps of greater relevance is the effect of HTLV-1 on T-lymphocytes, and in particular, its association with CD4+ lymphocytosis in HIV-1 co-infected patients.

Table 1. CD4+ and HIV viral load monitoring (2002 - 2009)

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4+ count (cells/μl)</th>
<th>CD4+ (%)</th>
<th>HIV-1 viral load (copies/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2002</td>
<td>794</td>
<td>15.0</td>
<td>19 365</td>
</tr>
<tr>
<td>September 2002</td>
<td>6 043</td>
<td>15.6</td>
<td>59 900</td>
</tr>
<tr>
<td>March 2003</td>
<td>4 891</td>
<td>13.9</td>
<td>31 400</td>
</tr>
<tr>
<td>September 2003</td>
<td>7 775</td>
<td>17.0</td>
<td>37 200</td>
</tr>
<tr>
<td>November 2003</td>
<td>7 799</td>
<td>21.0</td>
<td>58 300</td>
</tr>
<tr>
<td>June 2004</td>
<td>5 893</td>
<td>15.0</td>
<td>252 000</td>
</tr>
<tr>
<td>April 2006</td>
<td>13 820</td>
<td>23.1</td>
<td>133 281</td>
</tr>
<tr>
<td>September 2008</td>
<td>12 731</td>
<td>23.6</td>
<td>1 226 897</td>
</tr>
<tr>
<td>January 2009</td>
<td>2 875</td>
<td>73.0</td>
<td>494 510</td>
</tr>
<tr>
<td>April 2009</td>
<td>6 939</td>
<td>72.0</td>
<td>1 920</td>
</tr>
<tr>
<td>October 2009</td>
<td>1 973</td>
<td>61.1</td>
<td>Undetectable (&lt;20)</td>
</tr>
</tbody>
</table>
In general, lymphocytosis can be classified as belonging to one of two groups: either a reactive polyclonal proliferation, which can be caused by a variety of infective agents, hypersensitivity reactions, autoimmune conditions and splenectomy, or a clonal expansion as a result of a lymphoproliferative disorder.

In the context of HIV co-infection, lymphocytosis has been described during early seroconversion associated with CMV, as well as in HIV/HTLV-1 co-infection where CD4+ lymphocytosis can be caused by both a reactive or clonal expansion. Consequently, patients with untreated HIV who are co-infected with HTLV-1 show a dissociation between immunological and virological markers. That is to say, HIV-1/HTLV-1 co-infected patients have been found to progress to AIDS with a high HIV viral load, but in the presence of a normal or higher than normal CD4+ count (both absolute and percentage).[2,3] A recent study in Mozambique demonstrated that co-infected pre-HAART adult patients were seven times more likely to have CD4+ counts >500 cells/μl (median 525 cells/μl) than HIV mono-infected patients.[19] However, as these CD4+ cells are likely to be functionally altered, infected with HIV-1-infected peripheral blood mononuclear cells from immortalisation on account of its higher activation pattern, CD4+ lymphocyte counts in HIV-1/HTLV-1 co-infected patients cannot be considered to be a reliable marker of immunological competence.[13] Furthermore, CD4+ counts can be dramatically raised on account of ATLL (i.e. clonal expansion), which occurs in ≤5% of HTLV-1 infections.[20] As most cases of ATLL develop in individuals infected early in life through breastfeeding,[21] it is probable that our patient was already infected with HTLV-1 when he first presented in 2002 with a CD4+ count of 794 cells/μl. Whether he was infected with ATLL, HAM/TSP or infective dermatitis.

More research is needed to understand the epidemiology of HTLV-1 infection in Southern Africa; not only with regard to co-infections such as HIV-1/ HTLV-1 and TR/ HTLV-1, but also in terms of the wider public health impact, including implications for PMTCT practices and safety of the blood supply.

References