Human T-Cell Lymphotrophic Virus Type 1 Myelopathy/Tropical Spastic Paraparesis in a 65-Year-Old Man

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Human T-cell lymphotrophic virus type 1/type 2 (HTLV-1/HTLV-2) are type C retroviruses that are transmitted via sexual contact and blood products and from mother to child during breastfeeding. Most persons with HTLV-1 or HTLV-2 infection remain asymptomatic. However, HTLV-1 is known to cause adult T-cell leukemia and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP). Because HTLV infection in the United States is uncommon, these 2 diseases are rarely diagnosed. We present a case of HAM/TSP in a man who initially presented with unilateral lower extremity weakness.

CASE PRESENTATION
Initial Presentation and History

A 65-year-old African American man presented to the emergency department with left lower extremity weakness, which was initially diagnosed as a cerebrovascular accident. Two months later, the patient experienced increasing right lower extremity weakness, which progressed to bilateral lower extremity spastic paraparesis over the next month. The total time from initial presentation to the development of spastic paraparesis was 3 months. The patient denied sensory deficit, involvement of the upper extremities, and bowel or bladder incontinence. Pertinent past medical history included hypertension, diabetes mellitus, congestive heart failure, chronic renal failure, atrial fibrillation, and pacemaker implant for tachycardia-bradycardia syndrome.

The patient was born in the United States and was a resident of Louisiana. He denied travel, injection drug abuse, or blood transfusions. The patient also initially denied history of possible sexual exposure, but further questioning revealed previous contact with sex workers.

Physical Examination

On physical examination during the second presentation, the patient was a healthy-appearing man in no acute distress. Cardiovascular examination revealed an irregular rhythm consistent with atrial fibrillation, and a II/VI systolic ejection murmur was auscultated over the left upper sternal border and right upper sternal border. Digital rectal examination revealed normal sphincter tone. The neurologic examination was notable for staggering gait and slight dragging of the left lower extremity. Motor strength was 5/5 in the upper extremities bilaterally, 1/5 in the flexor muscles of the lower extremities, and 3–4/5 in the extensor muscles. Light touch, position sense, and pinprick sensation were intact bilaterally in the upper and lower extremities. Deep tendon reflexes were normal in the upper extremities, but hyperreflexia (3–4+) was present in the lower extremities. Babinski sign was present bilaterally.

Laboratory and Radiographic Studies

Laboratory results for the case patient are shown in the Table. Thyroid-stimulating hormone, folate, vitamin B₁₂, and vitamin B₆ were normal. Serum meningeal-encephalomyelitis panel was negative except for positive cytomegalovirus IgG antibodies, herpes simplex virus type 1 and type 2 IgG antibodies, and mumps IgG antibodies. Epstein-Barr virus (EBV) serologies were positive for EBV viral capsid antigen IgG antibody and negative for EBV viral capsid antigen IgM antibody. Serum HTLV-1/HTLV-2 enzyme-linked immunosorbent assay (ELISA) testing was positive, and HIV-1/HIV-2 was negative. HTLV-1 immunoblot was positive, whereas HTLV-2 immunoblot was negative. Computed tomography scan of the head without contrast and computed tomography myelogram of the cervical, thoracic, and lumbar spine were normal. Magnetic resonance imaging (MRI) could not be performed due to previous pacemaker placement. Based on these findings, the patient was
diagnosed with HAM/TSP (confirmed by Western blot test) caused by HTLV-1 infection.

Treatment and Outcome

Because of the lack of efficacy of available treatments, no specific treatment was provided. The patient was discharged to a nursing home with bilateral spastic paraparesis, which neither progressed nor improved during 18 months of follow-up.

DISCUSSION

Epidemiology

HTLV-1 infection is prevalent in the southwestern islands of Japan, where 20% of the adult population is seropositive; it is also found in the Caribbean, including the West Indies, northern South America, the southeast United States, Central and West Africa, Melanesia, the Middle East, and India. HTLV-1 isolates from different parts of the world share 92% to 97% homology, which suggests a high degree of conserved sequences. HTLV-1 is closely associated with HTLV-2, and although HTLV-1 infection appears to be present in disparate parts of the world, both types possibly share a common geographic origin. It is speculated that nonhuman primates may represent a natural reservoir of the HTLV-1 virus.

The HTLV-2 virus is endemic in Amerindian and pygmy tribes. Molecular subtypes indicate an origin within humans in Africa or South America. The virus started spreading among intravenous drug users in the United States and Europe during the 1970s, and it appears that the virus has reached the general population to a small degree through secondary sexual transmission. HTLV-2 has been linked to HAM/TSP in a few published case reports. It has also been suggested that HTLV-2 is associated with lymphoproliferative disorders, increased incidence of pneumonia, bronchitis, and inflammatory diseases such as arthritis.

Routes of Transmission

HTLV-1 and HTLV-2 are transmitted through sexual intercourse, blood products, or from mother to child via breastfeeding. Male-to-female transmission via sexual intercourse is the most common route of transmission of HTLV. There is a 61% likelihood that a woman will become infected after 10 years of sexual contact compared with 0.4% for men. The risk of viral transmission increases with high viral load, high titers of anti-HTLV-1 antibodies, and the presence of genital ulcers. Semen may be the main carrier of the virus because mononuclear cells containing the virus have been found in semen. Of note, HIV and HTLV (types 1 or 2) coinfections occur frequently in endemic areas.

HTLV-1 is also strongly associated with blood cells, but very low infectious titers have been found in plasma. Therefore, HTLV-1 is very easily transmitted by cellular blood components but not by plasma. Some studies suggest that storing red blood cells for 14 days or more prior to transfusion decreases the transmission rate to zero, which could be due to the destruction of T-lymphocytes during storage. In the United States, screening of donated blood for HTLV-1 has been routine since 1988.

The most common route of mother-to-child transmission for both HTLV-1 and HTLV-2 is through breastfeeding. The mechanism of transfer is by lymphocytes in the breast milk. Transmission occurs in 15% to 20% of children born to infected mothers. The risk of transmission increases if the mother has a high viral load and high antibody titers. Intrauterine transfer is rare. In addition, children with seropositive fathers but seronegative mothers generally do not

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (× 10³/µL)</td>
<td>9.81</td>
<td>3.4–9.2</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>47.4</td>
<td>43–75</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>38.7</td>
<td>15–44</td>
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<tr>
<td>Monocytes (%)</td>
<td>10.6</td>
<td>4–12</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.8</td>
<td>0–6</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.5</td>
<td>0–1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.9</td>
<td>12.6–16.6</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>46.3</td>
<td>39–49</td>
</tr>
<tr>
<td>Platelet count (× 10³/µL)</td>
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<td>142–405</td>
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<tr>
<td>Mean corpuscular volume (fl)</td>
<td>77.6</td>
<td>80–99</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>408</td>
<td>55–170</td>
</tr>
<tr>
<td>VDRL test</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>RPR test</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>—</td>
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Cerebrospinal fluid

<table>
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<tr>
<th>Laboratory Test</th>
<th>Result</th>
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</tr>
</thead>
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<tr>
<td>White blood cell (mm³)</td>
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<td>Red blood cell (mm³)</td>
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<tr>
<td>Lymphocytes (%)</td>
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<td>Monocytes (%)</td>
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<td>Glucose (mg/dL)</td>
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<td>Protein (mg/dL)</td>
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<tr>
<td>Myelin basic protein (ng/mL)</td>
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<td>&lt; 3</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>38.3</td>
<td>0.48–5.86</td>
</tr>
</tbody>
</table>

ANA = antinuclear antibody; RPR = rapid plasmag reagin; VDRL = Venereal Disease Research Laboratory.
become infected. Refraining from breastfeeding for a short duration (<7 months) may prevent transmission in endemic areas.\textsuperscript{1,6,17,21,22}

HTLV-1 infection is more prevalent among women, with a female-to-male ratio of 2:1.\textsuperscript{3,7,17,19} It has been noted that seropositivity is clustered within families in endemic areas,\textsuperscript{23} suggesting that the major routes of transfer are from mother to child and from male to female. Close contact during extended periods of time seems to be required for transfer of infected T-cells.

Pathophysiology

The demyelination that occurs in HTLV-1 infection appears to be caused by CD8+ mononuclear lymphoid cells, which infiltrate the perivascular and parenchymal space causing myelin and axonal destruction.\textsuperscript{24,25} Furthermore, new evidence suggests involvement of CD4+ cells.\textsuperscript{26} Parenchymal degeneration of the brain has also been described, but HTLV-1 has not been shown to infect or replicate in central nervous system (CNS) cells in vivo. Two major models have been presented to explain the mechanisms by which HTLV-1 causes HAM. The autoimmune model suggests that the HTLV-1 infection activates autoreactive T-cells, which in turn cause destructive changes in the CNS. The cytotoxic model states that the HTLV-1 virus infects glial cells, which initiates a cytotoxic immune response against these cells, thereby causing demyelination. HTLV-1 virus mainly infects CD4+ T cells, but some infected CD8+ cells have been found.\textsuperscript{17}

Clinical Presentation

Available data suggests that HTLV-1 and HTLV-2 are lifelong infections and that most infected persons are asymptomatic.\textsuperscript{3,11,17,23} In HTLV-1 carriers, the lifetime incidence of HAM/TSP is less than 5%, and onset of symptoms is usually in the fourth decade of life. HAM is a progressive demyelinating disease that affects the white matter of the CNS, including the spinal cord. HAM/TSP usually presents at a younger age, has a slow onset, and often is associated with variable degrees of sensory and proprioceptive defects as well as bladder dysfunction.\textsuperscript{2,17,18} Common presenting symptoms of HAM include motor weakness in the lower extremities and gait disturbance. For unknown reasons, the lower extremities are more often involved than the upper extremities.

The case patient represents a somewhat atypical presentation of HTLV-1 (HAM/TSP), and the differential diagnosis included transverse myelitis (cytomegalovirus, herpes simplex virus 1 and 2), multiple sclerosis, and mass lesions in the CNS. Our patient developed symptoms in his seventh decade and had a rapid progression to spastic paraparesis over a 3-month period without sensory deficits or bowel or bladder dysfunction.

Diagnostic Evaluation

In patients with HAM, MRI of the brain and spinal cord can reveal normal findings or show nonspecific atrophy and brain lesions. These lesions can resemble lesions seen in multiple sclerosis. The cerebrospinal fluid (CSF) of patients with HAM contains elevated protein and immunoglobulin; oligoclonal bands are also frequently seen. In peripheral blood and CSF, atypical lymphocytes resembling adult T-cell leukemia/lymphoma may also be found,\textsuperscript{7,17,27} but complete blood counts are otherwise normal. The case patient had elevated myelin basic protein in CSF (Table).

The testing algorithm for HTLV-1 resembles that for HIV-1. The initial test is a screening ELISA followed by confirmation with Western blot testing. ELISA does not differentiate HTLV-1 from HTLV-2; therefore, a specific HTLV-1/2 immunoblot or polymerase chain reaction should be performed to distinguish between the 2 infections. In a large study by Thorstensson et al\textsuperscript{28} comparing the sensitivity and specificity of ELISA, Western blot, and polymerase chain reaction for detecting HTLV infection, the highest sensitivities for detecting both HTLV-1 and HTLV-2 virus were obtained using combination ELISA methodology. Other studies\textsuperscript{29,30} found that ELISA and Western blot testing were sensitive for detecting and confirming HTLV infection.

Treatment

There is no standard treatment for HTLV-1 at present. However, some of the advances made in the treatment of HIV may become relevant for the treatment of HTLV-1. Plasmapheresis,\textsuperscript{31} corticosteroids,\textsuperscript{32} cyclophosphamide,\textsuperscript{33} and interferon-\(\alpha\)\textsuperscript{34} have produced only transient responses. Danazol, an anabolic steroid, has been reported to improve gait and bladder function in patients with HAM/TSP. Corticosteroids and danazol are currently the most commonly used treatment modalities in patients with HAM.\textsuperscript{7,24} Other investigational approaches for the treatment of HAM/TSP include zidovudine, anti-Tac antibodies directed against CD25 interleukin-2 receptor \(\alpha\)-chain, and interferon-\(\beta\) 1a therapy.\textsuperscript{25}

CONCLUSION

HTLV-1 infection is uncommon in the United States, and the 2 diseases associated with HTLV-1, adult T-cell leukemia/lymphoma and HAM/TSP, are rarely diagnosed in the United States. Although HTLV-1 and
HTLV-2 have similar routes of transmission, the 2 types have different pathophysiologic characteristics. Patients with HAM/TSP (a result of HTLV-I infection) typically present with lower extremity weakness and gait disturbances, and moderate to severe spasticity and bladder and bowel dysfunction may also be seen. Treatment options for HTLV-I are limited, as corticosteroids, plasmapheresis, cyclophosphamide, danazol, and interferon-α have had minimal effects.

REFERENCES


29. Caterino-de-Araujo A, de los Santos-Fortuna E, Melero


