Clinical and Immunological Findings in HTLV-III Infection

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Abstract

Clinical, immunological, microbiological, virological, and lifestyle parameters were followed in 200 homosexual men living in Finland. The subjects were seen at 3- to 6-month intervals starting in summer 1983. Human T-cell lymphotropic virus III (HTLV-III) antibodies detected by enzyme immunoassay and confirmed by Western blotting were seen in 18 (9%) of the cases. Initially two cases had acquired immunodeficiency syndrome, three had acquired immunodeficiency syndrome-related complex, three had lymphadenopathy syndrome, and ten were asymptomatic. During the follow-up two asymptomatic cases developed lymphadenopathy syndrome and three developed enlarged lymph nodes. Immunological studies revealed decreased T-helper cell values and/or T-helper/suppressor ratios in all clinical categories, the findings being more severe and progressive in the symptomatic cases. The finding most clearly distinguishing HTLV-III antibody positive cases from the antibody negative ones was a decreased response to a specific recall antigen, purified protein derivative of tuberculoprotein. Responses to mitogens phytohemagglutinin and pokeweed mitogen were also decreased, but to a lesser extent. The primary immunological defect associated with helper T-cell infection by HTLV-III thus seems to be loss of antigen specific immune responses. It is suggested that this is the result of previous antigenic stimulation of HTLV-III infected T-helper cells and that the cellular destruction is associated with initial mitotic activity.

Introduction

It has now been established that the primary cause for AIDS3 is an infection with a variant of HTLV-III. Antibodies to HTLV-III are frequently found in cases with AIDS, ARC, or LAS (1) but also in asymptomatic homosexual men (2). It would therefore be important to know whether all HTLV-III antibody positive cases even if not meeting the criteria for AIDS, ARC, or LAS have clinical or laboratory signs of ongoing HTLV-III infection.

We have followed a group of 200 homosexual men for 8-16 months and monitored their clinical, microbial, immunological, and lifestyle parameters. In the present paper we describe the spectrum of clinical findings in the HTLV-III antibody positive individuals and relate these to the immunological findings.

Subjects and Methods

Subjects. A group of 200 male homosexual volunteers participated in a prospective study starting in summer 1983 in Helsinki, Finland. Informed consent was obtained from each individual. Sexual practices and clinical histories were ascertained and a clinical study was performed at admission and at 3-6 month intervals.

Laboratory Tests. Antibodies to HTLV-III were assessed by EIA and Western blotting as described previously (3, 4). Immunological studies included measurements of proliferative responses to PHA, pokeweed mitogen, and PPD and analysis of the T-lymphocyte subsets, as described previously (5).

Results

Clinical Findings. Eighteen of the 200 cases had or developed antibodies to HTLV-III. The clinical picture and relevant laboratory findings are presented in Table 1. Two subjects were found to have clinically fulminant AIDS, three had ARC, and three had LAS. During the follow-up two of the asymptomatic cases developed LAS and three developed large, extrascapular lymph nodes, a finding characteristic of HTLV-III infection (Table 2).

HTLV-III Antibodies. The antibody titers varied in individual cases from very low (1:100) to very high (1:1,670,000). In the two AIDS cases and in two cases with very low initial titers a decrease of titers was seen during the follow-up. The remaining cases showed consistently increasing titers.

Immunological Findings. The HTLV-III antibody positive group differed from the antibody negative one in both T-cell subset values as well as in the functional assays. The T-helper to suppressor ratio was significantly decreased. This was mainly due to a decrease in T-helper cells in the antibody positive group in contrast to elevation of T-suppressor cells in the antibody negative group (Chart 1). A significant decrease in the functional assays and especially in the proliferative response to a specific antigen, PPD, was seen only in HTLV-III positive cases with a T-helper:suppressor ratio below 1.0 (mean, 2 SD of the controls) (Chart 1).

Immune abnormalities were seen in all disease categories but they were more frequent and severe in the symptomatic cases. There was also a faster progression in the latter cases during the follow-up (Chart 2). β2-Microglobulin values were elevated mostly in the symptomatic cases (Chart 3).

The decreased response to PPD was the most significant functional abnormality in the HTLV-III antibody positive group. All cases with a low PHA response had likewise a low PPD response while cases with low PPD response often had normal PHA responses (Chart 4). Similarly low PPD responses were seen even with normal T-helper values (Chart 5) while the low

1 Presented at the HTLV Symposium, December 6 and 7, 1984, Bethesda, MD.
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: AIDS, acquired immunodeficiency syndrome; HTLV-III, human T-cell lymphotropic virus III; ARC, acquired immunodeficiency syndrome-related complex; LAS, lymphadenopathy syndrome; PHA, phytohemagglutinin; PPD, purified protein derivative of tuberculoprotein.
Clinical picture, HTLV-III antibody titers, and immunological findings in HTLV-III antibody homosexual men at admission and after 8-16 months follow-up

Table 1
Clinical diagnosis at admission and 10-16 months follow-up

<table>
<thead>
<tr>
<th>Case</th>
<th>HTLV-III titer at admission</th>
<th>T-helper cells at 10-16 months</th>
<th>Mantoux test</th>
<th>Circulating Immune Complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 mo 8-16 mo</td>
<td>0 mo 8-16 mo</td>
<td>0 mo 8-16 mo</td>
<td>2 tuberculin units</td>
</tr>
<tr>
<td>1</td>
<td>Well</td>
<td>100  Negative</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Well</td>
<td>400  Negative</td>
<td>1.2</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Well</td>
<td>100,000 200,000</td>
<td>0.4</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Well</td>
<td>5,000 18,000</td>
<td>0.6</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Well</td>
<td>400,000 1,670,000</td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Well</td>
<td>Linh Negative</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Well</td>
<td>LNN 100,000 550,000</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Well</td>
<td>LNN Negative 6,000</td>
<td>6.0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Well</td>
<td>LAS 510,000 1,370,000</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Well</td>
<td>LAS Negative 17,000</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>LAS</td>
<td>LAS 230,000 310,000</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>LAS</td>
<td>LAS 405,000</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>LAS</td>
<td>LAS 140,000</td>
<td>0.8</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>ARC</td>
<td>ARC 260,000 290,000</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>ARC</td>
<td>ARC 480,000</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>ARC</td>
<td>ARC 242,000</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>AIDS</td>
<td>AIDS 1,100,000 1,030,000</td>
<td>0.2</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>AIDS</td>
<td>Dead 23,000 7,000</td>
<td>0.4</td>
<td>-</td>
</tr>
</tbody>
</table>

* Conglutinin binding, Clq binding, or RF-enzyme immunoassay.
* Enlarged lymph nodes not meeting the criteria for LAS.
* Treated with leukocyte α-interferon.

Table 2
Presence of enlarged lymph nodes in the study group of homosexual men

<table>
<thead>
<tr>
<th>HTLV-III antibody (n = 22)</th>
<th>Submandibular</th>
<th>Occipital</th>
<th>Jugular</th>
<th>Axillar</th>
<th>Inguinal</th>
<th>Extra submandibular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>57</td>
<td>14</td>
<td>26</td>
<td>52</td>
<td>19</td>
<td>57</td>
</tr>
<tr>
<td>Negative</td>
<td>45</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

* P < 0.01.

Discussion

With the availability of a serological test to identify individuals who have been infected with HTLV-III, it has become clear that clinically fulminant AIDS is an ultimate end point of a disease with a variable clinical spectrum. Our findings in an unselected group of Finnish homosexual men are in keeping with this view. More than half of the HTLV-III antibody positive cases were asymptomatic at admission. Most of these cases had, however, signs of an ongoing infection with affected immune parameters. The question therefore arises whether all these clinical cate-
CLINICAL AND IMMUNOLOGICAL FINDINGS IN HTLV-III INFECTION

...a general tendency to a progressive deterioration. Moreover five of the ten initially asymptomatic cases became symptomatic during the follow-up period. HTLV-III infection thus seems to be a progressive deteriorating disease with variation in the intensity of its manifestations.

**Chart 3.** α₂-microglobulin values (mg/liter) in HTLV-III antibody positive homosexual men without symptoms (WELL) or with AIDS, ARC, or LAS.

**Chart 4.** PHA and PPD responses in HTLV-III antibody positive homosexual men without symptoms or with AIDS, ARC, or LAS. 0, asymptomatic; 0, LAS; U, ARC; 5, AIDS.

**Chart 5.** T-helper values and PPD responses in HTLV-III antibody positive homosexual men without symptoms or with AIDS, ARC, or LAS. 0, asymptomatic; 0, LAS; U, ARC; 5, AIDS.

**Chart 6.** T-helper values and PHA responses in HTLV-III antibody positive homosexual men without symptoms or with AIDS, ARC, or LAS. 0, asymptomatic; 0, LAS; U, ARC; 5, AIDS.

**Chart 7.** Destruction of HTLV-III infected and expansion of noninfected antigen specific T-helper (Th) cell clone as a result of stimulation by corresponding antigen.

**NON-INFECTED LYMPHOCYTE POPULATION**

**HTLV-III INFECTED LYMPHOCYTE POPULATION**

Death of the infected cells

Death of the infected cells

Proliferation of antigen 1 specific Th helper cell clone

Proliferation of antigen 2 specific Th helper cell clone

Clonal expansion

Clonal expansion

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of the symptoms and in the speed of the clinical progression in individual cases.

What are the factors that regulate the clinical outcome of the HTLV-III infection? Host factors such as other infections and/or immunization against alloantigens might be involved in addition to the dose and virulence of the infective agent. In our material high EBV titer and signs of previous HBV infection were associated with the strongest immunosuppression in the HTLV-III antibody positive group (5). There was also an increased preference for anal sex, thus facilitating allogeneic immunization to sperm antigens.

It is of interest to note that many of the cofactors which might regulate HTLV-III infection are T-cell mitogens. Proliferation of antigen specific T-helper cells on the other hand could lead to progression of the infection or activation of a latent virus in two ways: (a) proliferation could regulate the expression of a receptor for HTLV-III and (b) the virus replication in the infected cell could be associated with replication of cellular DNA. On these grounds it is possible to present a model for the progression of immunosuppression in HTLV-III infection where any foreign antigen will initially cause a proliferation of the corresponding T-cell clone but later leads to its destruction (Chart 7). The reaction to foreign microbial antigens would in HTLV-III infected individuals thus differ from that in the noninfected ones; in the latter case immunization will lead to the expansion of the antigen specific clone whereas in the HTLV-III infected individuals the corresponding clone would be definitively destroyed. With repeated infections with a variety of microbial organisms the immune repertoire against microbes would be lost one by one. Our preliminary findings with one microbial antigen, PPD, are in keeping with this hypothesis.

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References


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