Pathogenesis of B Cell Lymphoma in a Patient With AIDS


Lymphoma occurs at increased frequency in patients with the acquired immunodeficiency syndrome (AIDS). We studied, using serologic and molecular techniques, one such lymphoma for (a) evidence of infection with human T lymphotropic virus, type III (HTLV-III), and Epstein-Barr virus (EBV), (b) monoclonal rearrangement of immunoglobulin and T cell receptor genes, and (c) rearrangement of the c-myc oncogene. Immunoglobulin and T cell receptor gene studies demonstrated that the tumor was of monoclonal B cell origin. Similar to cases of Burkitt’s lymphoma unrelated to AIDS, there were DNA sequences in the lymphoma that hybridized to EBV-specific probes and demonstrated evidence of c-myc rearrangement. HTLV-III sequences were not detected in the malignant B cells. The pathogenesis of some B cell neoplasms in patients with the syndrome may involve transformation by EBV and deregulation of oncogene expression without direct infection of the malignant B cells by HTLV-III.

Support: Supported by grants No. A121161, A121129, 1-F32-HL06725-01, NHLBI 1-P60-HL38774-01, and 1-R01-HD18128-01 from the National Institutes of Health and a grant from the American Cancer Society. J.L.S. is an established investigator of the American Heart Association.

Submitted: June 20, 1985; accepted Sept 10, 1985.

Address reprint requests to Dr Jerome E. Groopman, Division of Hematology-Oncology, New England Deaconess Hospital, 110 Francis St, Boston, MA 02215.

© 1986 by Grune & Stratton, Inc.

612


From www.bloodjournal.org by guest on August 30, 2017. For personal use only.
revealed evidence for rearrangement at the heavy chain locus and probable deletion of both kappa light chain loci. Examination of the T cell receptor alpha and beta chain loci revealed exclusively the germline configuration with no evidence for clonal rearrangement (data not shown). This pattern is most consistent with monoclonal proliferation of B cell origin and of lambda light chain type. These results were in agreement with the immunofluorescent studies.

Serologic studies indicated antibodies to EBV early, nuclear, and capsid antigens, cytomegalovirus, and HTLV-III (Table 1). Antibodies to HTLV types I or II were not present. The tumor tissue expressed EBV nuclear antigen detected by immunofluorescence. Southern analysis revealed sequences related to EBV in the B cell lymphoma (Fig 2) but no hybridizing sequences using probes for cytomegalovirus, HTLV-III, HTLV-I, and HTLV-II. Rearrangement near the c-myc gene was also detected by Southern analysis (Fig 3).

DISCUSSION

B cell lymphomas occur with increased frequency in a variety of hosts with inherited or acquired deficiencies of the cellular immune system. Considerable epidemiologic and molecular biologic data suggest that some of these B cell lymphomas are associated with the presence of circular EBV genome and possibly integration of EBV into host genome. Polyclonal B cell hyperplasia is frequently found in lymph nodes of patients with AIDS or AIDS-related complex. In some cases, there appears to be an initial

Table 1. Laboratory Studies

<table>
<thead>
<tr>
<th>Serology</th>
<th>1:80</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV-EA</td>
<td>1:40</td>
</tr>
<tr>
<td>EBV-VCA</td>
<td>1:160</td>
</tr>
<tr>
<td>EBNA</td>
<td>1:128</td>
</tr>
<tr>
<td>CMV-CF</td>
<td>+</td>
</tr>
<tr>
<td>HTLV-III-ELISA</td>
<td>-</td>
</tr>
<tr>
<td>HTLV-III-Western blot</td>
<td>+</td>
</tr>
</tbody>
</table>

Molecular Studies on Lymphoma DNA

| EBV                     | +    |
| HTLV-III                | -    |
| Immunoglobulin rearrangement | +   |
| T cell antigen receptor rearrangement | -   |

EBV, Epstein-Barr virus; EA, early antigen; VCA, viral capsid antigen; EBNA, EBV-nuclear antigen; CMV-CF, cytomegalovirus complement fixation; HTLV-III-ELISA, enzyme-linked immunosorbent assays.
polyclonal activation of B cells, followed by emergence of a monoclonal neoplasm. HTLV-III is the primary etiologic agent in AIDS. The T4 antigen, or a closely related membrane antigen, appears to be necessary for entry and permissive infection of HTLV-III in T lymphocytes. Because some activated B cells express the T4 antigen and, in vitro, HTLV-III can infect T4-bearing lymphoblastoid cell lines transformed by EBV, it is possible that HTLV-III could directly infect in vivo activated B cells and play a primary pathogenetic role in the development of B cell neoplasia in AIDS. Our study of this case argues against such a model. There were no sequences related to HTLV-III in the B cell lymphoma, despite clear serologic evidence of HTLV-III infection in the host. A more likely model, based on our study, would be the emergence of an EBV-transformed B cell clone resulting from impaired cellular “immunologic surveillance” due to infection of T cells by HTLV-III.

Serologic studies in AIDS demonstrate high titers of antibodies to EBV antigens, suggesting reactivation of this virus in some patients. Previous case reports have indicated chromosomal translocations t(8;14) and t(8;22) in B cell lymphoma in AIDS. Such translocations occur in endemic (African) and nonendemic Burkitt’s lymphoma. Karyotype was not done in our case, but DNA rearrangement near the c-myc gene was detected. The c-myc oncogene is located on chromosome 8 and is rearranged in Burkitt’s lymphoma unrelated to AIDS. The pathogenesis of some B cell lymphoma in AIDS may involve initial polyclonal expansion of the B cell population due to reactivation of EBV with subsequent emergence of a transformed monoclonal population characterized by chromosomal rearrangement and disordered regulation of the c-myc oncogene. The emergence of the transformed clone may be facilitated by HTLV-III infection and impaired immune surveillance.

REFERENCES


22. Dagleish AG, Beverly PC, Clapham PR, Crawford DH, Greaves MF, Weiss RA: The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 312:763, 1984


Pathogenesis of B cell lymphoma in a patient with AIDS

JE Groopman, JL Sullivan, C Mulder, D Ginsburg, SH Orkin, CJ O'Hara, K Falchuk, F Wong-Staal and RC Gallo