Aggressive Non-Hodgkin's Lymphomas in Immunocompromised Homosexual Males

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During the period from 1981 through 1984, 14 immunocompromised homosexual males with intermediate or high-grade non-Hodgkin's lymphoma were seen at University of Texas M.D. Anderson Hospital and Tumor Institute. Six patients had diffuse large-cell lymphoma, seven had diffuse undifferentiated lymphoma, and one had unclassifiable lymphoma that suggested large-cell lymphoma. Eight patients had the acquired immunodeficiency syndrome (AIDS) and five had the AIDS-related complex. Kaposi's sarcoma was initially present in four patients and developed later in two others. The patients with diffuse large-cell lymphoma were characterized by more severely altered immune parameters, multicentric brain mass lesions, pretherapy opportunistic infections, lower perfor-

**Materials and Methods**

From 1981 to 1984, 237 adult male patients with large-cell lymphoma (LCL) and 14 adult male patients with diffuse undifferentiated lymphoma (DUL) were evaluated at University of Texas M.D. Anderson Hospital and Tumor Institute. Fourteen of these provided histories of homosexual preference and life-style. Routine staging procedures were used in these patients, including chest radiography, lymphangiography, abdominal computerized tomography (CT), bone marrow biopsy, and other indicated tests. For the purpose of this study, the pathological findings were reviewed by one of us (J.J.B.). All patients were classified (Table 1) according to the modified Rappaport classification used at M.D. Anderson Hospital, where the term large-cell lymphoma is used for the type formerly designated histiocytic lymphoma. 19 Brief nonimmunologic clinical data of patients No. 1 through 5, 7 through 12, and 14 were included in Ziegler's national study of homosexual males with lymphomas. 20

The following immunologic studies (Table 2) were performed as described previously. 21 While helper (T4) and suppressor (T8) surface markers and surface immunoglobulins were determined on peripheral blood lymphocytes in an Ortho Spectrum III cell analyzer, (Ortho Diagnostics, Raritan, NJ), and the number of lymphocytes with such markers was expressed as total numbers per cubic micrometer. Delayed-type hypersensitivity was measured using a conventional battery of skin test antigens, including dermatophyton, Candida, streptococcus, mumps, and purified protein derivative of tuberculin protein. Cytomegalovirus (CMV) titers were measured by an IgG immunofluorescent antibody technique using the whole virus as substrate, and Epstein-Barr virus (EBV) titers were measured by an IgG immunofluorescent antibody to the viral capsid antigen. Immunoperoxidase staining for B and T cell markers was performed on frozen section slides in five cases.

Various multiagent combination chemotherapeutic regimens were used in most patients (Table 3). Patients with CNS involvement underwent 3,000 rad total-brain irradiation. In addition, patients with either CNS or bone marrow involvement received intrathecal injections of methotrexate and cytosine arabinoside, usually through Omaya reservoirs if CNS disease was demonstrated.

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RESULTS

Most of the 14 male homosexual patients had histories of multiple sexual partners and recreational drug use. Thirteen patients were from Texas and one was from New Mexico. Several had recently traveled to New York or San Francisco. Median age of all patients was 35 years (Table 1).

Histopathological review revealed that all patients had intermediate to high-grade lymphomas, as classified in the current “Working Formulation.” All were morphologically consistent with B cell neoplasms, with tissue immunoperoxidase confirmation in four DUL specimens, and with positive surface immunoglobulins on cell suspension in three DUL specimens. Chromosomal studies confirmed a t(8;14) translocation in four DUL patients and a t(8;22) translocation in one patient. Four of seven patients with DUL had histories of generalized lymphadenopathy for several months before the diagnosis of lymphoma. In three, the lymphadenopathy was histologically consistent with the typical reactive follicular and sinusoidal changes described by Guarda et al in patients with AIDS or ARC.

The presenting data are shown in Table 1. LCL patients No. 1 through 5 had the unusual findings of multicentric brain lesions, documented by biopsy of mass lesions on CT scan in five patients and at autopsy in one; LCL patient No. 6 had a unifocal brain mass confirmed as lymphoma by premortem biopsy. LCL patients No. 1 and 2 had lymphoma documented histologically at autopsy as mass lung lesions. LCL in patient No. 1 was confirmed by liver biopsy at the time of diagnosis. Additional extranodal sites documented at autopsy in patient No. 1 included the heart, kidneys, and adrenal glands. Bone marrow involvement with lymphoma has not been seen in any of the LCL patients. KS was present in patients No. 1, 2, 3, and 6 at the time of diagnosis of LCL, all of whom had stomach and skin KS lesions; patient No. 2 also had lung, hard palate, and other KS intestinal lesions, and patient No. 6 also had rectal and hepatic lesions. There were no complete remissions of lymphoma or KS resulting from chemotherapy or radiotherapy in the LCL patients, although patients No. 3 and 5 had partial regression of brain masses of short duration. All died within six months of diagnosis (Table 3).

The DUL patients had the usual sites of involvement of
lymph nodes and bone marrow, similar to those described in other DUL patients without immunodeficiency, although one patient had tonsillar lesions, an unusual site for DUL. Only two of the seven DUL patients (No. 11 and 13) have had CNS disease, which presented not as mass lesions of the brain, but as meningeal involvement. Patients No. 9, 11, and 13 had bone marrow involvement, and two of these had leukemic cells in the peripheral blood on initial evaluation. Brain abscess, esophagitis, giardiasis, Pneumocystis pneumonia, and CMV chorioretinitis and proctitis were seen in only two (No. 7 and 10) of the DUL patients, but no debulking procedures were done. Patient No. 11 also had liver involvement with lymphoma. While four of the DUL patients had histories of reactive peripheral lymphadenopathy, only one of these had nodal lymphoma alone at presentation. KS was seen in only two (No. 7 and 10) of the DUL patients, occurring 15 months and 11 months after the diagnosis of lymphoma; it was localized in the hard palate in patient No. 7 and to the skin and small bowel in patient No. 10 and responded completely to interferon treatment in both patients. All of the DUL patients responded to combination chemotherapy, and five of the seven entered complete remission. Five of these are alive at 19, 19, 35, seven, and 0.5 months from diagnosis. Multiple opportunistic infections preceding and during chemotherapy were documented in five of the six LCL patients, including Candida and Toxoplasma brain abscesses, atypical Mycobacterium brain abscess, Cryptosporidia diarrhea, Candida esophagitis, giardiasis, Pneumocystis and CMV pneumonia, and CMV chorioretinitis and proctitis. None of the DUL patients had opportunistic infections before chemotherapy, and the infections that developed during myelosuppressive chemotherapy responded well to antibiotics.

Results of pretreatment immunologic studies are shown in Table 2. All patients had evidence of altered cellular immunity, shown by inverted helper-suppressor T lymphocyte ratios, low absolute numbers of helper T lymphocytes, and decreased delayed hypersensitivity skin test reactivity. The abnormalities were generally much more pronounced in the LCL patients, who had a median helper-suppressor ratio of only 0.1 and who were completely anergic in five cases. Quantitative immunoglobulins were normal or only slightly diffusely increased or decreased in the 11 patients tested. Eleven patients had serologic evidence of preceding or active CMV infections, and all 14 had elevated EBV titers. Five patients had positive serologic tests for the hepatitis B surface antigen.

Three additional male homosexual patients with indolent lymphomas involving extranodal sites, including earlobes, kidneys, and bone marrow, were also seen at our institution since 1981. These are described in detail elsewhere.

### DISCUSSION

KS has been recognized as part of AIDS in homosexual males since it was first defined by the Centers for Disease Control in 1981. In 1982 the first cases of lymphomas in this population were reported by Doll and List and Ziegler et al. Since that time several additional cases of aggressive lymphomas in immunocompromised homosexual males have been reported. The total recent experience is analyzed, our findings reinforce the high percentage of LCL and undifferentiated lymphomas in homosexual patients, many of whom have a high frequency of involvement of unusual extranodal sites, such as the CNS.

Our population of 14 homosexual patients with intermediate to high-grade lymphomas may be classified into two major groups. In the first group are the LCL patients who had multicentric brain mass lesions and who had a high incidence of severe opportunistic infections before the diagnosis of lymphoma, with laboratory evidence of profound T cell dysfunction. These individuals had poor pretreatment performance statuses, did not tolerate treatment well, and had poor responses to chemotherapy or radiotherapy. All patients died of progressive disease or opportunistic infection within six months of diagnosis.

The second group of patients includes those with undifferentiated lymphomas of the Burkitt's or non-Burkitt's subtype. The extranodal sites were generally those expected for this type of lymphoma, such as bowel and bone marrow, with no mass lesions of the brain documented. Most of these patients had histories of generalized reactive lymphadenopathy, which recurred in some concomitantly with the appearance of the lymphomas. The excellent performance statuses, absence of pretherapy opportunistic infections, and relatively less impaired immune systems, compared with those of the LCL patients, allowed them to tolerate combination chemotherapy well. Bone marrow recovery was usually adequate to allow chemotherapy to be given at the desired time intervals. In contrast to the LCL patients, five of seven DUL patients

### Table 3. Response of Lymphoma to Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Histology</th>
<th>Treatment</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LCL</td>
<td>MBV</td>
<td>No</td>
<td>Died 1 mo</td>
</tr>
<tr>
<td>2</td>
<td>LCL</td>
<td>Cranial XRT, VP-16</td>
<td>No</td>
<td>Died 2 wk</td>
</tr>
<tr>
<td>3</td>
<td>LCL</td>
<td>Cranial XRT, AM</td>
<td>PR</td>
<td>Died 5 mo</td>
</tr>
<tr>
<td>4</td>
<td>LCL</td>
<td>Cranial XRT</td>
<td>No</td>
<td>Died 3 mo</td>
</tr>
<tr>
<td>5</td>
<td>LCL</td>
<td>Cranial XRT, CHOP-B</td>
<td>PR</td>
<td>Died 3 mo</td>
</tr>
<tr>
<td>6</td>
<td>LCL (IBS)</td>
<td>Cranial XRT</td>
<td>No</td>
<td>Died 2 wk</td>
</tr>
<tr>
<td>7</td>
<td>DUL</td>
<td>CHOP-M</td>
<td>CR</td>
<td>35 + mo</td>
</tr>
<tr>
<td>8</td>
<td>DUL</td>
<td>MCOAP</td>
<td>CR</td>
<td>19 + mo</td>
</tr>
<tr>
<td>9</td>
<td>DUL</td>
<td>XRT, IMVP-16</td>
<td>CR</td>
<td>Died 12 mo</td>
</tr>
<tr>
<td>10</td>
<td>DUL</td>
<td>MCOAP</td>
<td>CR</td>
<td>19 + mo</td>
</tr>
<tr>
<td>11</td>
<td>DUL</td>
<td>Cranial XRT, VAD</td>
<td>PR</td>
<td>Died 3 mo</td>
</tr>
<tr>
<td>12</td>
<td>DUL</td>
<td>MCOAP</td>
<td>CR</td>
<td>7 + mo</td>
</tr>
<tr>
<td>13</td>
<td>DUL</td>
<td>VAD</td>
<td>PR</td>
<td>2 + wk</td>
</tr>
<tr>
<td>14</td>
<td>UNCL</td>
<td>XRT, CHOP-B</td>
<td>CR</td>
<td>13 + mo</td>
</tr>
</tbody>
</table>

Included in the individual regimens: MBV, methotrexate; bleomycin, velban; VP-16, etoposide; AM, cytosine arabinoside; methotrexate; CHOP-B, cyclophosphamide, Adriamycin, vincristine, prednisone, bleomycin; CHOP-M, cyclophosphamide, Adriamycin, vincristine, prednisone, methotrexate; MCOAP and IMVP-16, methotrexate, cytoxan, vincristine, cytosine arabinoside, prednisone, ifosfamide, etoposide, Adriamycin, bleomycin; and VAD, vincristine, Adriamycin, Decadron. PR, partial remission; CR, complete remission; XRT, irradiation.

LCL, diffuse large-cell lymphoma; IBS, immunoblastic sarcoma; DUL, diffuse undifferentiated lymphoma; UNCL, unclassified lymphoma.
achieved complete remission and three are surviving free of lymphoma more than 19 months after diagnosis.

The high frequency of extranodal sites and the incidence of KS seen in this group of 14 homosexual patients with non-Hodgkin's lymphomas are distinctly unusual. The increased frequency of primary CNS lymphoma has been noted in several previous small series of patients and represented a markedly increased incidence in our own population of lymphoma patients. While four patients in our present series presented with isolated brain lesions, there had only been five other individuals with primary brain LCL seen in our institution in the past 30 years, where an average of 60 previously untreated cases of LCL are seen each year. The brain was the only site of involvement at diagnosis in only 0.2% of patients in a previously reported study of more than 12,000 lymphoma patients.26 Although there is a slightly increased incidence of lymphoreticular disorders reported in patients with KS,23 we had seen no other instances of KS in our lymphoma population in the past ten years. Our results indicate that the incidence of Burkitt's-like DUL has also increased in the homosexual population, since six of the 23 adult patients with DUL seen at our institution since 1981 have been homosexual males. Others have suggested similar conclusions.10,17,19

It is interesting to speculate on the reasons for development of certain types of lymphomas in our immunosuppressed homosexual male population. The LCL patients share several features with cardiac or renal allograft transplant recipients or patients with the congenital Wisqott-Aldrich syndrome, who have severe deficiencies of cell-mediated immunity.28-31 Transplantation patients have up to a 350 times increased incidence of clinically aggressive LCLs, often of the brain and lung, within one year of immunosuppression after transplantation. This may be due to chronic viral antigenic stimulation in the presence of a severely altered immune surveillance system. The EBV genome has recently been demonstrated in the tumor tissue of at least one CNS lymphoma,24 and it has been proposed that the brain may occasionally act as an immunologic "sanctuary site,"33,34 where latent herpes-type viruses could activate B cells that escape the influence of systemic immune control.

In contrast to the LCL patients, our DUL population had somewhat less evidence of immunosuppression, with the presence of reactive lymphadenopathy indicating some reserve of immune function, and they tended to develop generalized lymphoma that was sensitive to chemotherapy. This may be analogous to the occasional progression from infectious mononucleosis to lymphoma-like illnesses.35 While the suppressor lymphocytes that are activated during EBV-associated infectious mononucleosis may help to control the polyclonal lymphocyte proliferation, the controlling signals occasionally fail and a monoclonal malignancy develops. It is possible that the multiple antigenic stimuli thought to contribute to development of AIDS (such as the CMV, EBV, and other herpes viruses; the human T cell leukemia-lymphoma virus (HTLV-III)36 and the related T-cell lymphotropic virus37; recreational drugs38; and sperm antigens) may alter the immune system in such a way that the B cells become more susceptible to the proliferative effects of antigen stimuli39 and are eventually transformed into neoplastic clones. Such permissive roles have been proposed for the malarial organism in the development of African Burkitt's lymphoma40 and CMV in the pathogenesis of KS.6,7,41 Chromosomal abnormalities may also be involved, as in five of our patients, allowing for oncogenic transformation of B cells. All five patients had translocations involving chromosome No. 8, the location of the c-myc oncogene.42 The lymphoma tissues of all of these patients should be studied extensively, as they may serve as models of human oncogenesis in the future.

In summary, we stress the unusual extranodal involvement of non-Hodgkin's lymphomas in immunosuppressed homosexual males, particularly the high incidence of CNS involvement, and recommend that appropriate diagnostic workups, including brain and lung biopsies, be performed to distinguish lymphomas from the lesions of opportunistic infections that occur in these patients. Also, while there has been some concern that chemotherapy for the lymphomas in this population would be ineffective and poorly tolerated because of the complicating immunodeficient state, we demonstrate that therapy can be well tolerated and may lead to an improved survival rate in the subset of patients without severe preceding or concomitant opportunistic infections.

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