Epidemiological and Biological Study of Acquired Immunodeficiency Syndrome-related Lymphoma in the County of Los Angeles: Preliminary Results


Abstract

A population-based case control study of intermediate- and high-grade lymphoma in the County of Los Angeles, CA, was initiated in 1989. Human immunodeficiency virus (HIV)-positive lymphoma patients are compared to HIV-negative lymphoma patients, to HIV-positive controls with acquired immunodeficiency syndrome but without lymphoma, and to HIV-positive asymptomatic individuals. The HIV-negative lymphoma cases are compared to neighborhood controls, who are matched in terms of age, sex, race/ethnicity, and socioeconomic status. All cases are reviewed for pathology by a single group of pathologists. All cases and controls are studied for HIV, Epstein-Barr virus (EBV), and human herpesvirus 6 antigens and antibodies. Tissues from HIV-positive and -negative cases are studied for immunoglobulin gene rearrangement, presence of EBV and HIV, c-myc oncogene rearrangements, and karyotypic analysis. To date, with 294 lymphoma cases and 181 control cases interviewed, high-grade lymphoma has been diagnosed in 82% of the HIV-positive cases versus 40% of the HIV-negative cases (P = 0.001). Although elevated titers of EBV-viral capsid antigen were demonstrated in 82% of HIV-positive versus 50% of HIV-negative lymphoma cases, the geometric mean titer of EBV-viral capsid antigen is similar among HIV-positive lymphoma cases and HIV-positive controls. The geometric mean titer of human herpesvirus 6 antibodies was similar in HIV-positive and HIV-negative lymphoma cases and in the control populations. Monoclonality was demonstrated in all cases of lymphoma. EBV genome was demonstrated within lymphoma DNA in 68% of HIV-positive and 15% of HIV-negative lymphoma cases. Further study will be required to elucidate the full mechanisms of pathogenesis of the acquired immunodeficiency syndrome-related lymphomas.

Introduction

AIDS was first recognized in 1981, in young, homosexual men from New York, San Francisco, and Los Angeles with opportunistic infections, Kaposis sarcoma, and primary CNS lymphoma. Although unusual cases of systemic malignant lymphoma were also recognized at that time, statistically significant increases were not apparent until 1985 (1), at which time the Centers for Disease Control changed the case definition of AIDS to include the high-grade, B-cell lymphomas (2). Inclusion of intermediate-grade large cell lymphoma, occurring in individuals infected by HIV was later added to the case definition of AIDS.

Pathologically, the AIDS-related lymphomas consist primarily of high-grade, B-cell disease, including small noncleaved and immunoblastic lymphomas, occurring in approximately 80-90% of reported cases (3-6). Other designations for small noncleaved lymphoma include "undifferentiated lymphoma," which may be of "Burkitt" or "non-Burkitt" type; the immunoblastic category was termed "diffuse histiocytic lymphoma" in older classification schemes. In large series of reports of lymphomas published prior to the HIV epidemic, approximately 10% of cases were made up of these high-grade, B-cell types (7).

The AIDS-related lymphomas are also distinct in terms of the widespread extent of disease at initial presentation, occurring in approximately 80-90% of patients (3-5). In large series studied prior to 1981, extranodal lymphoma was reported in approximately 40% of individuals (8). Virtually any site may be involved, with propensity for CNS, gastrointestinal tract, and bone marrow, as well as involvement in rather unusual sites including anus and rectum, oral cavity, and heart (3-5).

Patients with AIDS-related lymphoma also appear distinct in terms of their response to therapy and subsequent survival. Significant toxicity has been described after the use of multiagent chemotherapy, and median survival has been approximately 6 months (9).

In an attempt to further characterize the lymphomas associated with HIV infection and to determine potential etiological and pathological mechanisms of disease, a case-control study of intermediate- and high-grade, B-cell lymphoma in the County of Los Angeles was initiated in 1989. Preliminary results are reported herein.

Materials and Methods

All cases are identified by CSP, which is the population-based tumor registry which identifies all histologically confirmed cancers among the 8.9 million residents of Los Angeles County, CA. The CSP was initiated in 1970 and became part of the California Statewide Cancer Registry system in 1987.

Rapid case ascertainment methods are used, and all cases of high- or intermediate-grade lymphoma, consecutively identified by the CSP, are eligible for study if they are between the ages of 18 and 75 years and speak English or Spanish. After each case is identified, the physician of record is notified, and permission is asked to contact the patient. The patient is then contacted directly, and "accrued," if consent is obtained. Serum is obtained for analysis of exposure to HIV, to EBV, and to HHV-6. Whole blood is collected for analysis of HLA type and for later analysis of peripheral blood lymphocytes. Tissue blocks are obtained from each patient, as well as fresh lymphomatous tissues, whenever possible. These tissues are studied for HIV and EBV, using the PCR technique, as well as Southern blot analysis, which is also used to determine immunoglobulin gene rearrangement to ascertain the genotypic monoclonality of the lesions. Presence of c-myc rearrangements and p53 gene mutations are also ascertained. Karyotypic analysis of fresh tissues is performed to determine specific chromosomal abnormalities. All cases are reviewed by a central group of pathologists who use the Working Formulation for Clinical Usage, as well as the Lukes-Collins classification scheme.

Primary "cases" are considered to be those individuals with pathologically confirmed intermediate- or high-grade lymphoma, who are...
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found to be HIV seropositive. Control 1 cases are patients with intermediate- or high-grade lymphoma, who are HIV seronegative. Control 2 cases are those with HIV infection and AIDS, as defined by illness other than lymphoma; and control 3 cases are those with asymptomatic HIV infection and no evidence of AIDS; these latter two groups of controls are individually matched by age (within 3 years), sex, race/ethnicity, socioeconomic status and AIDS risk group to our HIV-positive lymphoma cases. A separate control group of neighborhood controls is identified for our HIV-negative lymphoma patients; these are control 3 cases are those with asymptomatic infection lymphoma cases. A separate control group of neighborhood controls is identified for our HIV-negative lymphoma patients; these are control 3 cases are those with asymptomatic infection lymphoma cases. 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tumors, which may arise from on-going B-cell proliferation, induced by HIV directly or indirectly by cytokine release, by EBV, or by other factors, in the setting of immune dysregulation induced by HIV and chronic, antigenic stimulation due to the multiple infections and other exposures which occur commonly in these patients. Epidemiological data from the current study, when analyzed completely, may help to identify these exposures, which may serve as cofactors in the development of lymphomatous disease.

References

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