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# Lymphoma and Acquired Immunodeficiency Syndrome: Cytogenetic and Molecular Correlates

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THE acquired immunodeficiency syndrome (AIDS) continues to attract much scientific attention and has raised considerable public interest in recent months. A retrovirus, the human immunodeficiency virus (HIV, HTLV III/LAV), is believed to be the primary etiologic infective agent. This virus is particularly cytotoxic for the CD-4 T-lymphocyte (OKT4 helper/inducer T-cell) and renders discordant the well-orchestrated harmony of the immune system. This cacophony is best demonstrated within the cell-mediated compartment as patients develop secondary neoplasms and recalcitrant infections with viruses, protozoa, fungi and specific recurrent bacteria. Most affected patients suffer lethal infections with opportunistic pathogens and nearly half will develop neoplasms.

The neoplastic complications of AIDS are well-recognized. Recent reviews of AIDS-related malignancies show that nearly 95% of the neoplasms are either Kaposi's sarcoma (85% of male homosexuals) or non-Hodgkin's malignant lymphoma (4–10%). There has been a marked increase in the incidence of high-grade B cell lymphoma [1]. According to the newly revised guidelines of the Center for Disease Control (CDC), small non-cleaved (Burkitt or non-Burkitt type) lymphoma and immunoblastic sarcoma are accepted as diseases indicative of AIDS in HIV antibody seropositive patients [2]. Other neoplasms often reported lack epidemiologic confirmation and are therefore not included in the CDC case definition. They include Hodgkin's disease, cloacogenic anal carcinoma and squamous cell carcinoma of the head, neck and oral cavity [3, 4]. Since the first reported outbreak of Burkitt's-like lymphoma in homosexual men [1], the role of Epstein–Barr virus (EBV) and cytomegalovirus (CMV) in the etiology of these AIDS-related conditions has been pondered [5–7]. In a recent review on the subject, Levine [3] writes 'There is evidence suggesting a correlation between EBV and the high incidence of lymphomas, and the most plausible explantion for this is the ability of EBV to cause ongoing B-cell proliferation.' Other herpes viruses may also participate in the pathogenesis of these lymphomas but a definite relationship has not been established.

Features that distinguish AIDS-related lymphoma from *de novo* non-Hodgkin's lymphoma include: (a) younger patient population, (b) common extra-nodal presentation and (c) intermediate or high grade histology. Generally, patients have a rapidly progressive clinical course. In the majority of patients, complete responses to conventional combination chemotherapy are temporary [3].

As with most hematologic malignancies, chromosomal abnormalities found in patients with AIDS-related lymphoma have become the focus of recent investigation. Endemic (African) as well as nonendemic Burkitt's lymphoma (BL) cells are characterized by specific translocations that affect chromosomes 2, 8, 14 and 22 [5–8]. The most frequent of these translocations is t(8;14)-(q24;q32), while variant translocations t(2;8)-(p12;q24) and t(8;22)(q24;q11) seem to occur less

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often [5]. The genes responsible for immunoglobulin heavy chains, kappa light chains and lambda light chains have been mapped to chromosomes 14, 2 and 22 respectively. The juxtaposition of the c-*myc* oncogene by translocation to specific sites on these chromosomes results in unregulated transcriptional activation and monoclonal proliferation of B cell neoplasms [3, 5, 9].

Cytogenetic abnormalities reported in AIDS-related, high grade lymphomas include duplications and deletions of 1, 7, 9 and 12; and translocations involving chromosomes (1;9), (1;4), (1;19) and (10;14) [5–8]. While there appears to be no unequivocally consistent, non-random chromosomal abnormalities associated with AIDS, certain changes seen in the high-grade lymphomas can be incorporated into current classification schemes.

Chaganti *et al.* [5] described translocations in Burkitt's-like lymphoma (BLL) of homosexual men with AIDS. According to this early report BLL had identical translocations to those seen in BL [5]. Later, Whang-Peng *et al.* [6] described two more patients, one with an 8;14 and one with an 8;22 translocation and suggested that the incidence of t(8;22) may be increased in these patients. Additionally, they found abnormalities in both patients involving the long arm of chromosome 1. Abnormalities of chromosome 1 have been seen in association with other hematologic malignancies, including BL [10, 11]. In a review of cytogenetic and histologic correlations in malignant lymphoma, breaks on chromosome 1 were unique and did not correlate with histologic subtypes. Bands 1p34–36 and 1q22–24 were only encountered with additional abnormalities [9]. Interestingly, the cellular oncogenes c-*src* and c-*ski* have been mapped to these sites respectively [9, 12, 13]. Abramson and Verma [14] reported the finding of a 48,XX,+7,+12,t(10;14)(q4;q32) in a patient with intermediate grade lymphoma in transition from a low-grade histology. Recently, Kosmo *et al.* [15] reported a case with trisomy 12 in Burkitt-like lymphoma and suggested an association with AIDS. Even patients with normal Karyotypes should be evaluated using an HIV probe [16] because they too have gene rearrangement. These unique findings raise many questions [17].

In both animal and human tumor cell systems a variety of oncogenes have been identified. The list continues to grow and nearly three dozen cellular oncogenes have been mapped [12]. A cause and effect relationship has yet to be established for chromosomal changes and molecular oncology in the pathogenesis of AIDS-related high grade lymphoma. It is extremely important to report as many abnormalities as are found in this group of patients. Cytogenetic findings may prove to be a useful tool for assessing prognosis as well as current and future forms of therapeutic intervention among patients with a poor clinical outlook. It is not unreasonable to suggest that the amalgamation of clinical, genetic and molecular data may provide a clearer picture of disease pathogenesis and the basis for an effective vaccine. A chromosome registry of this type might lead to a better subtyping of this syndrome.

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