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Perspectives and Commentaries

The Epidemic of AIDS Virus Infection, What is the Interest for Oncologists?

NATHAN CLUMECK*
Division of Infectious Diseases, St Pierre University Hospital, Brussels, Belgium

THE ACQUIRED immunodeficiency syndrome has emerged in mid-1981 as what appears now to be an extraordinary disease that provides insights into the working of the immune system and the origin of cancer. The etiology of AIDS is a cytopathic human T-lymphocytotropic retrovirus named HTLV-3/LAV that manifests selective infectivity for the helper/inducer subset of T-cells (T4 or Leu3). The immune systems of patients with AIDS exhibits a profound lymphopenia, with a lowering of the ratio of helper cells to suppressor cells; functional abnormalities of T-lymphocytes such as decreased proliferative responses to mitogens and antigens, decreased virus-specific cytotoxic lymphocyte function and decreased ability to provide help to B-lymphocytes; functional abnormalities of B-lymphocytes and decreased natural killer cell activity. The underlying immune deficiency is the common denominator for the development of the opportunistic infections and tumors characteristic of the syndrome.

In Western countries, AIDS victims are mainly male homosexuals or bisexuals (73%) or heterosexual IV drug users (17%) [1]. In developing countries AIDS affects heterosexually active people without known risk factors [2]. The occurrence of cancer (mainly Kaposi's sarcoma) in one-third of male homosexuals in contrast with 5–7% among heterosexuals with AIDS suggests that cofactors related to homosexuality could be involved in the pathogenesis of cancer among AIDS patients. Among these cofactors, recreational drugs such as nitrite amyl and exposure to CMV, EBV and hepatitis B have been advocated. Table 1 summarizes the cancers noted among homosexuals and their link to possible oncogenic DNA viruses. Data from cancer registries covering 10% of United States have shown a dramatic increase in Kaposi's sarcoma and non-Hodgkin lymphomas during the period 1983–1984 as compared to the pre-AIDS period (1973–1979), among never-married, 20–40-year-old men [4]. During the same periods no change was noted in trends of cancer unrelated to AIDS. The pattern of increase in Kaposi's sarcoma parallels the increase in HTLV-3/LAV seropositivity during recent years. Kaposi's sarcoma is probably one of the first human cancers to be occurring in epidemic form.

The existence of a relationship between immune deficiency and neoplasia was recognized more than a decade before the present AIDS epidemic [5]. Of all the tumors developing in immune-deficient individuals, by far the most common are those of the lymphoid system. Non-Hodgkin's lymphomas represent 3–4% of all tumors of the general population but constitute 26% of the tumors arising in recipients of renal transplants and 71% in recipients of cardiac transplants. Kaposi's sarcoma, with an incidence of only 0.002% in the general population, occurs in 4.9% of transplant patients and is the malignancy most commonly seen in the AIDS

Table 1. Cancer among male homosexuals

Type	Potential oncogenic virus
Kaposi's sarcoma	Cytomegalic
Non-Hodgkin lymphoma	Epstein–Barr
Squamous cell carcinoma of the tongue	Herpes simplex type 1
Cloacogenic carcinoma of the rectum	Herpes simplex type 2 papilloma

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*Associate Professor and Chief.

victims [6]. In the course of Kaposi's sarcoma, additional tumors may develop in as many as 37% of patients, and of these, lymphoid tumors are 20 times more common than other tumors [7].

The current cases of lymphoma among HTLV-3/LAV-infected people are quite distinct from those observed in the immune-competent patient in relation to their location, histology, natural history, and response to treatment. In the future, there is no doubt that diagnosis of such lymphoma will lead oncologists to consider the possibility of HTLV-3/LAV infection in persons who do not present themselves as homosexual or bisexual.

Disease confined to lymph nodes is expected in the majority of lymphoma patients as noted among a group of 405 patients, in whom disease in lymph nodes alone was found in 6% [8]. In contrast, in patients with AIDS, lymphoma is mostly extranodal, with a high incidence of central nervous system involvement (between 30 and 42%), bone marrow and extra-abdominal involvement. Histologic types are of high grade categories with a reversed ratio of Hodgkin's lymphoma to non-Hodgkin's lymphoma. The phenotype is monoclonal B-cell, or non B- non-T-cell types without any T-cell lymphomas. The response to treatment and survival is disappointingly poor in the light of current therapy results in other patients with similar histologic subtypes of lymphoma. The poor prognosis is the result not of inadequate treatment but of severely impaired immunity [9, 10, 11].

The pathogenesis of this tumor may involve the immune deficiency state, genetic predisposition and chronic antigenic stimulation. Two of the 3 tumors studied by Ziegler were found to contain Epstein–Barr viral antigen [12]. A relation between EBV and monoclonal B-cell Burkitt lymphoma has been found in Africa [13], EBV viral genome sequences have been shown to be homologous to DNA sequences from Burkitt lymphoma cells. Recently, it has been demonstrated that there were DNA sequences in the lymphoma of a patient with AIDS that hybridized to EBV-specific probes. There was also evidence of deregulation of oncogene expression (*c-myc* rearrangement) without direct infection of the malignant B-cells by the AIDS virus [14]. In the setting of chronic antigenic stimulation and proliferation of B-lymphocytes, non-Hodgkin's lymphoma could result from chromosomal translocation and malignant transformation of B-lymphocytes that are immortalized by Epstein–Barr virus and escape T-cell control.

Thus under the conditions of HTLV-3/LAV infection it is possible that infection with, or reactivation of, latent EBV induces lymphoma. The lymphoid system in AIDS is doubly affected, being the target both of the initial viral infection that induces the immune deficiency and of the second viral infection that produces neoplasia. In this respect, the observation of seropositivity to HTLV-3/LAV and HTLV-1 among intravenous drug abusers reported by De Rossi *et al.*, is particularly interesting and intriguing.
intriguing.

HTLV-1 is a type C retrovirus which is the causative agent of adult T-cell leukemia/lymphoma (ATL), a malignant lymphoma that is endemic in southwestern Japan, the Caribbean, and the southeastern portion of the United States [15, 16, 17]. HTLV-1 is also prevalent in Africa where antibodies to HTLV-1 have been found in 3.7% of 161 blood donors and in two patients with lymphoproliferative disease in Nigeria [18, 19].

In all regions where clusters of ATL have been found, high titres of background infection in the normal population have been detected. Up to 15% of the population of the southern Japanese island of Kyushu has antibody titre to this virus [20]. Many people without leukemia manifest persistent antibodies to HTLV-1 and some harbour the virus in their peripheral blood T-cells [21]. Thus simple infection with HTLV-1 is not itself sufficient to induce ATL. HTLV-1 is tropic for T4 lymphocytes, the same target that HTLV-3/LAV, and results in their malignant transformation and uncontrolled proliferation. Double infections with HTLV-3/LAV and HTLV-1, as demonstrated by De Rossi *et al.*, raise fundamental questions in regard of the physiopathology of an unique target cell (T4 lymphocyte) submitted to the influence of viruses with opposite effects (cytolytic for HTLV-3/LAV and oncogenic for HTLV-1). Will these patients present further T-cell lymphoma, which has so far not been observed, by proliferation of subclasses of T4 cells or by T8 proliferation? Will the HTLV-1 infection balance the cytopathic effect of HTLV-3/LAV? Will the incubation period of ATL eventually be shortened by an underlying defect in the immune surveillance system? All these questions will need, in the future, considerable attention.

Another problem of particular concern is the existence of HTLV-1 seropositive among hemophiliacs who received blood products contaminated with HTLV-3/LAV. At the present time, compulsory screening of blood donors for HTLV-3/LAV antibodies has been adopted in most Western countries. The question remains now; should such screening also be compulsory for HTLV-1 antibody to prevent ATL? If yes, this certainly will be one of the numerous amazing and unexpected consequences of the AIDS epidemic.

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