Acquired immunodeficiency syndrome—associated malignancies

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Acquired immunodeficiency syndrome (AIDS)—associated malignancies are a concern to all physicians. Because patients usually are seen initially by nonspecialists, primary care physicians, especially, may find useful information about AIDS-related malignancy. Cancers remain a part of the clinical definition of AIDS. Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas are the malignancies most frequently seen in AIDS. Acquired immunodeficiency syndrome KS occurs in young men between 20 and 40 years of age, and involves the skin in more than 90% of patients. Visceral dissemination is common. The prognosis is related to immune functional status and the extent of disease involvement. Acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma is generally a B-cell malignancy. Advanced disease at presentation and proclivity for central nervous system involvement are characteristic. Knowledge of the common manifestations of these cancers, methods of diagnosis, and potential treatment options is important for physicians.

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As the number of human immunodeficiency virus (HIV)—infected individuals increases, and newer clinical manifestations of disease become apparent, it is important to have a working knowledge of the basic presentations of HIV infection and acquired immunodeficiency syndrome (AIDS). Malignancy, especially the heretofore unusual Kaposi's sarcoma (KS), was part of the initial clinical description and working definition of AIDS. As information has been collected, it has become apparent that cancer is a major clinical aspect of AIDS. The malignancies most frequently seen as clinical manifestations of AIDS are reviewed herein. A brief background of immunodeficient states in which malignancies may be seen is presented. Theoretical considerations regarding the cause of AIDS-associated malignancies and some therapeutic options are also presented.

Immunodeficiency and cancer

Malignancy associated with immunodeficient states is not new. Both congenital and acquired immunodeficiency conditions are associated with increased risk of malignancy.¹⁻⁴ Severe combined immunodeficiency syndrome (SCIDS), for example, is associated with malignancy; 1.5% of patients with SCIDS have cancer develop at a median age of 0.9 year. Deficiency of humoral and cellular immunity is found as a predisposing factor in organ transplant recipients in whom malignancy develops after treatment with immunosuppressive drugs (Table 1).

In AIDS, the cytopathic effects of HIV on T-helper-cell number and function result in

Table 1 Immunodeficient and Iatrogenic Immunodeficient States and Malignancy		
Disease/Condition	Immune defect	Cancer incidence, %
Immunodeficient states and malignancy		
Severe combined immunodeficiencies	B + T cell	1.5
Ataxia telangiectasia	B + T cell	12
Wiskott-Aldrich syndrome	B + T cell; monocyte	>15
Bruton hypogammaglobulinemia	B cell	0.7
Common variable immunodeficiency	B + T cell	2.5–8.5
Iatrogenic immunodeficient states and malignancy		
Renal transplant	B + T cell	6
Cardiac transplant	B + T cell	5 (lymphoma)

Table 2 Centers for Disease Control Acquired Immunodeficiency Syndrome Case Definition: Malignancies
With laboratory evidence of human immunodeficiency virus infection Kaposi's sarcoma at any age Lymphoma of the brain (primary) Non-Hodgkin's lymphoma of B-cell or unknown Immunologic phenotype and either: Small noncleaved lymphoma (Burkitt's or non-Burkitt's type) or Immunoblastic sarcoma
Without laboratory evidence regarding human immunodeficiency virus infection Kaposi's sarcoma affecting a patient < 60 years of age. Lymphoma of the brain (primary) affecting a patient < 60 years of age

profound immunodeficiency and dysregulation of both new antigenic responses and anamnestic responses.⁵⁻⁷ This central T-helper-cell loss is the primary immunodeficiency with which malignancy in AIDS is associated. Part of the Centers for Disease Control (Atlanta, Ga) definition of AIDS includes certain malignant neoplasms, with or without laboratory evidence of HIV infection (Table 2). The two most common malignancies are epidemic KS (EKS) and non-Hodgkin's lymphoma.

Kaposi's sarcoma

Kaposi's sarcoma is a malignant tumor thought to be of endothelial origin because of the demonstration of factor VIII antigen in association with the malignant cells.^{1,8,9} It is a multifocal disease that, at presentation, involves the skin in more than 90% of patients. The initial lesions, which may be palpable, are usually faintly discolored pink- to purple-hued areas of skin.¹⁰⁻¹² Unlike classic KS, EKS frequently occurs on the trunk, head and neck, or extremities (Fig 1). There is a predilection for the lesions of EKS to involve the helix of the ears, oral cavity, and soles of the feet¹ (Figs 2 and 3, left). In addition to truncal area disease, unusual manifestations include subungual involvement and involvement of the medial canthus of the eye (Fig 3, right). Noncutaneous involvement is frequent, with approxi-

mately 50% of patients having visceral disease at presentation. Lymph nodal and submucosal gastrointestinal disease is frequent, but EKS also has been described in the liver, lung, heart, brain, and genitourinary system. Pulmonary disease has been reported to have a particularly ominous prognosis.^{11,12}

The age at which EKS most frequently occurs is 20 to 40 years. Epidemic KS makes up approximately 30% to 40% of the cases of opportunistic infection in patients with AIDS who have KS, not mutually exclusive of other opportunistic infection manifestations of AIDS.^{1,10}

Epidemic KS as a manifestation of AIDS appears to be more frequent in homosexual/bisexual males than in intravenous (IV) drug users. It is therefore predominantly a male disease with an estimated male-female ratio of 50:1.¹

The diagnosis of EKS requires a biopsy specimen for histologic confirmation. The lesions are not microscopically distinct from the lesions of classic KS seen in older heterosexual males.

The histologic picture may be spindle cell or angiomatous within a reticular and collagen network.¹⁰ The presence of extravasated erythrocytes, hemosiderin, or phagocytized erythrocytes may help in establishing the histologic diagnosis. Although KS is a vascular

Figure 1. *Characteristic lesions of epidemic Kaposi's sarcoma. Extensive cutaneous involvement of the trunk with pigmented irregular ovoid lesions.*

Figure 2. *Kaposi's sarcoma of the soles of the feet is a characteristic location in patients with epidemic Kaposi's sarcoma.*

Figure 3. Unusual locations for epidemic Kaposi's sarcoma include helix of the ear (left) and medial canthus of the eye (right).

lesion, a biopsy does not result in excessive, unusual, or prolonged bleeding.

As in most malignancies, an assessment of tumor burden by clinical staging has been used in KS.¹³ Disease limited to one anatomic area of the skin is considered as being limited (stage I). In the most advanced stage (stage IV), KS involves the skin and visceral sites, such as the lung or liver. However useful clinically, prognosis is also related to absolute T-helper-cell number, T-helper/T-suppressor ratio, the presence of prior or current opportunistic infection, and anemia.^{1,14,15} Patients with opportunistic infection and very low T-helper-cell levels have the worst prognosis, with approximately 80% mortality by 12 to 24 months.^{14,16}

There are a variety of treatment options for EKS, including palliative radiation therapy, chemotherapy, and the use of biologic agents.¹⁷⁻²¹ At present, persons who have a good prognosis should probably not receive systemic therapy.²² For those with disseminated disease, local disability, and progressive clinical deterioration, there is no standard therapy. Although treatment in these individuals may palliate symptoms, there is no evidence that treatment has an impact on survival. On

the contrary, systemic multiagent chemotherapy may increase the risk of development of opportunistic infection.^{23,24} The most frequently used chemotherapy agents are the periwinkle alkaloids, vincristine, vinblastine, and etoposide (VP-16). Biologic agents, particularly interferon alfa and lymphoblastoid interferon, have been used with variable success in disease control. No long-term survival benefit has been attendant to these treatments.

Non-Hodgkin's lymphoma

In 1984, Ziegler and colleagues²⁴ called attention to the development of non-Hodgkin's lymphoma in homosexual men. Since that time, further description and clinical characterization have led to better recognition of AIDS-associated lymphomas.

These tumors are generally B-cell malignancies of an aggressive histologic nature, such as diffuse large-cell lymphoma or small non-cleaved-cell lymphomas of the Burkitt or non-Burkitt type.²⁴⁻²⁸ The clinical presentation is usually of advanced disease, ie, Ann Arbor stage III or IV, and approximately half the patients have symptoms of weight loss or fever not attributable to infection.²⁷ There is a pro-

clivity for these malignancies to occur at extranodal sites, especially the central nervous system, bone marrow, liver, lung, gastrointestinal tract, and heart.²⁶⁻²⁸

The cause of aggressive histologic B-cell neoplasms in patients with AIDS is speculative. A role has been suggested for Epstein-Barr virus infection, and cytomegalovirus and nitrites have been studied as potential cofactors.^{28,29}

Diagnosis can be established only by biopsy. In patients with AIDS who have altered neurologic function, assessment for a space-occupying CNS lesion should precede spinal fluid analysis for malignant cells, and a brain biopsy may be required to establish the cause of abnormal CNS function.

Patients with generalized lymphadenopathy associated with HIV infection pose a troublesome dilemma for the clinician; however, changes in lymph node size, new lymph node enlargement, and development of signs of visceral disease or B symptoms (fever, weight loss, and night sweats) should alert the clinician to a need for lymph node biopsy.

In general, systemic multiagent chemotherapy for AIDS-related malignant lymphomas has resulted in fewer complete remissions than in non-AIDS patients.^{28,30} Those who attain complete remission tend to have an early relapse, with CNS progression being a problem.³⁰ The development of opportunistic infections with increased risk of death is attendant to high-dose chemotherapy.

At present, no therapy can be considered standard for the treatment of these patients. In one study, the most significant prognostic factor for response to treatment was Karnofsky performance status.³⁰ Patients with AIDS-related lymphomas may also have KS prior to, or during, the course of their lymphomatous disease.²⁷

Practical considerations

From the foregoing, it is apparent that the diagnosis of malignancy in persons with AIDS requires histologic confirmation by biopsy.

In general, a biopsy specimen of a skin lesion is easily obtained by excision or punch biopsy techniques. The decision to obtain a biopsy specimen is dependent on the lesion char-

acteristics and the clinical history of the patient. If the patient has a known high-risk behavior or a previously known confirmed positive HIV test, then a biopsy specimen should be obtained sooner rather than later.

For lymphoma, whether or not to obtain a biopsy specimen is a more difficult decision because many HIV-infected individuals may have generalized lymphadenopathy. Nevertheless, lymph nodes ≥ 2.5 cm in diameter (except in inguinal lymph nodes), nodes that are "stony hard," nodes that are enlarging, or nodes that are grown together (matted) or that have adhered to other structures should be considered for excisional biopsy.

Human immunodeficiency virus testing for establishing the diagnosis of AIDS is not necessary in those patients < 60 years of age who have KS or primary brain lymphoma. Alternatively, patients may want to be tested to determine if they are HIV infected so that they may provide this information to those who they may feel may be at risk from intimate exposure.

In some locales, HIV testing requires written informed consent, and this may preclude testing in some patients with lymphoma. Knowledge of HIV test results in individuals with lymphoma may provide information that may be of prognostic value (HIV-associated lymphomas generally have a poorer prognosis than non-HIV-associated disease).

Human immunodeficiency virus testing is not indicated in the majority of patients with common malignancies such as colon, lung, or breast cancer. Even though these patients may be HIV infected, these malignancies are not AIDS associated.

At the present time, testing for HIV remains a patient's decision and a physician's recommendation.

Summary

Neoplastic complications of HIV infection are not limited to large urban medical centers.²⁶ Most patients will have complaints of rash, lymph node enlargement, fever, or weight loss. The majority of patients will not be seen first by oncologists or infectious disease specialists, but by primary care clinicians.

A careful clinical history to assess for high-risk behavior may be helpful in assessing the clinical index of suspicion for AIDS-associated malignancies.³¹ As with all cancers, diagnosis is dependent on adequate biopsy and careful assessment of histopathologic findings. There are, at present, no "standard" modes of therapy. Familiarity with local resources for clinical trial participation will be helpful for the physician caring for patients with AIDS-related cancers.

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