

• UPDATE IN CLINICAL MEDICINE •

AIDS-Related Malignancies: Revisited

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Since the first reports between the association of Human Immunodeficiency Virus (HIV) infection and neoplasia, there has been a dramatic change in the incidence and epidemiology of AIDS-related malignancies. Kaposi sarcoma (KS), non-Hodgkin's lymphomas (NHL), and cervical cancer are classified by the Centers for Disease Control and Prevention (CDC) as AIDS-defining malignancies. However, since the availability of highly active combination antiretroviral therapy (cART), especially protease inhibitors, there has been a steady increase in non-AIDS defining malignancies, such as Hodgkin's lymphoma (HL), lung cancer, hepatocellular cancer, anal cancer and others and a decline in AIDS-defining neoplasias. Although the emergence of non-AIDS defining cancers could be a result of longer life expectancy and due to a better control of HIV, toxic habits and co-infection with other viruses such as hepatitis B, hepatitis C and human papilloma virus (HPV) could play an important role. The interactions of cART and incomplete immune reconstitution could be other factors explaining the increase in non-AIDS defining cancers. These emerging non-AIDS defining malignancies present a new challenge in the care of patients with HIV infection, and require optimal treatment protocols that take into consideration the interaction between cART and systemic chemotherapy. We review the current status of AIDS-related malignancies, its pathophysiology, epidemiology and management with emphasis in the changing patterns of presentation. [*P R Health Sci J* 2010;1:70-75]

Key words: Acquired Immunodeficiency Disease, Kaposi's sarcoma, Non-Hodgkin's lymphoma, Protease inhibitors

Since 1981, when the Human Immunodeficiency Virus (HIV) was first linked to the development of Kaposi's sarcoma (KS) in predominantly homosexual men in San Francisco, USA, there has been a dramatic change in the neoplastic manifestations of patient with Acquired Immunodeficiency Disease (AIDS). The Center for Disease Control (CDC) established non-Hodgkin's lymphomas (NHL) and cervical cancer as AIDS-associated tumors since 1993 (1). However, since the availability of protease inhibitors in 1996, there has been an increase in non-AIDS defining cancers among people with AIDS, such as Hodgkin's lymphoma (HL), lung cancer, hepatocellular cancer and anal cancer (2). Engel's et al., in a series of AIDS patients in the United States from 1980 to 2002 estimated the standardized incidence ratios (SIRs) of AIDS and non-AIDS defining cancers relative to the general population rates (Table 1) (3). This method compares the observed number of cases arising in a group under investigation (patients with HIV infection) with the number expected to occur on the basis of general population rates. In contrast, the control of the HIV infection with highly active combination antiretroviral therapy (cART), has led to a significant decrease in AIDS defining malignancies such as Kaposi's sarcoma and non-Hodgkin's

lymphomas. Although the emergence of non-AIDS defining cancers could be a result of the longer life expectancy of patients infected with HIV, other factors such as the interaction of cART with other risk factors such as co-infection with hepatitis B and C viruses and toxic habits such as cigarette consumption could play a role in these changing trends. Patients with HIV infection have more aggressive tumors, present at a younger age and are less often cured. In France in the year 2005, one third of deaths in HIV patients resulted from malignancy (42% AIDS-defining cancers and 58% non-AIDS-defining) (4). In New York City, the survival of cancer among AIDS patients has been reported as follows: 2 year survival of 58% for Kaposi's sarcoma, 29% for primary brain lymphoma, 10% for lung cancer, 55% for Hodgkin's disease, 76% for anal cancer and 64% for cervical cancer (5).

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Table 1. Standardized- Incidence Ratios for AIDS defining and non-AIDS defining cancers

AIDS defining		//	non-AIDS defining			
NHL	KS	Cervical cancer	HL	Lung cancer	Anal cancer	Liver cancer
22.6	3640	5.3	13.6	2.6	19.6	3.3

(adapted from Spano JD, Costagliola D, Katlama C, et al. AIDS-related malignancies: state of the art and therapeutic challenges. *Journal of Clinical Oncology* 2008;26:4835 Copyright the American Society of Oncology)

Basal cell skin cancer, mainly on the trunk, conjunctival cancer especially in subSaharan Africa, sarcomas, melanomas, germ cell tumors, multiple myeloma and leukemias have been also consistently described as emerging neoplasms in patients with AIDS (6-7). These emerging reports of non-AIDS defining malignancies present a new challenge in the care of patients with HIV infection and require optimal treatment protocols in order to control these conditions.

We will review the current status of AIDS- related malignancies and the changing patterns of presentation as the highly active antiretroviral therapy have controlled better the immunodeficiency disease but have not impacted equally the control of non-AIDS defining malignancies. Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical cancer, Hodgkin's lymphoma, anal cancer, lung cancer and other malignancies in the setting of AIDS will also be discussed.

Kaposi's sarcoma (KS)

KS was the first AIDS defining malignancy in 1981. Its incidence has decreased dramatically but still is higher in homosexual men and in people from subSaharan origin and remains the second most frequent tumor observed in HIV-infected patients. KS is an indolent vascular tumor that has been subdivided into epidemiologic variants, including classic KS, African endemic KS, iatrogenic KS and epidemic AIDS-associated KS (8). Human Herpesvirus 8 (HHV-8) is found in tissues from all forms of KS and suggests a central role for the virus in the development and etiology of all KS types (9, 10). HHV-8 also has been associated to multicentric Castleman's disease and primary effusion lymphoma in patients with AIDS. Epidemic KS presents in approximately 21% of homosexual men with AIDS. It presents with pink-violaceous macules involving the face, chest, and oral mucosa (Figure 1) (8). The hard palate and ocular conjunctiva are frequently involved and progresses in an orderly fashion to a more generalized skin disease with lymph node involvement and gastrointestinal disease.

Effective cART is the first step of therapy and has resulted in a worldwide dramatic decline in the development of KS among patients with AIDS. HHV-8 produces a viral G-protein-coupled receptor protein (vGPCR protein) with paracrine and autocrine activities producing several proliferative cytokines and

angiogenesis factors that result in tumor development (Figure 2) (11). Signaling by vGPCR activates Akt, which induces cell transformation. The vGPCR also results in the production of a variety of other factors: interleukin-8, growth-related protein alpha, interleukin -6, interleukin -1- beta, and tumor necrosis factor alpha. HHV-8 may remain in a latent phase for many years, but the interaction with HIV TAT protein and a profound immunosuppressed state transforms the virus into a lytic state that invades the host's endothelial cells (12-14). Once the host cell is infected with the HHV-8, molecular targeted therapies could have a role in the control of inflammation and angiogenesis (Figure 3) (2, 15). For limited skin lesions, local therapy with liquid nitrogen, intralesional therapy and local treatment with alitretinoin has been useful (16). Systemic therapy for visceral or rapidly progressive disease involves drugs such as liposomal doxorubicin, paclitaxel, interferon-alpha, vinblastine, vincristine, bleomycin and others (17-21). Recent advances in the understanding of KS pathogenesis via the infection of endothelial cells by HHV-8 have led to the development of new targeted agents such as metalloproteinase inhibitors, angiogenesis inhibitors (thalidomide), tyrosine kinase inhibitors (imatinib mesylate), and mammalian target of rapamycin inhibitors (2, 15).

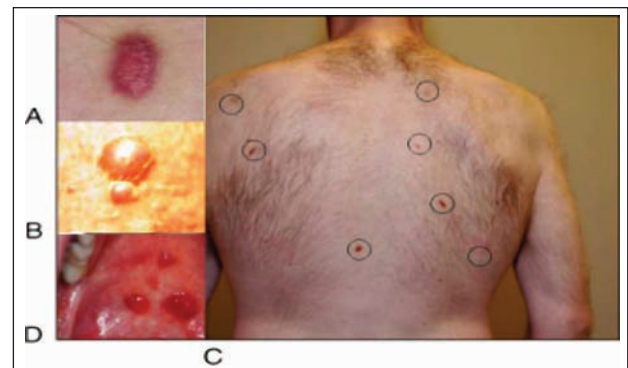


Figure 1. KS lesions. A. Plaque lesion, B. Nodular lesions, C. Near symmetric distribution of lesions on the trunk, D. Lesions on the hard palate, (originally published in Ambinder RF. HIV-associated malignancies in Abeloff MD, Armitage JO, Niederhube JE, Kastan MD, McKenna WG, eds. *Clinical Oncology*, 3rd edition, Elsevier Inc. 2004;2650. Copyright Elsevier).

Non-Hodgkin's lymphomas (NHL)

NHL is the most common AIDS-defining malignancy, even in patients who have adequate response to cART (22). Most cases are high-grade such as diffuse large B-cell and Burkitt's lymphoma. Frequently the lymphomas are extranodal and central nervous system involvement is common for which prophylaxis is warranted as part of their treatment. The CD-4 count is predictive of the development of NHL (Figure 4) (23). A more recently described entity, the primary effusion lymphoma, is a peculiar subset of large B-cell lymphoma

that mainly occurs in AIDS patients and is characterized by HHV-8 infection of the tumor clone and by a tropism to the serous body cavities (24-26). Morphologically, they have anaplastic immunoblastic features and display a certain degree of plasma-cell differentiation (Figure 5) (27). Primary effusion lymphoma occurs as a late manifestation of HIV infection. Patients have a poor clinical outcome and a shorter overall survival (6 months) when compared with other high grade NHL (28). Primary central nervous system lymphomas, associated to Epstein-Barr virus, have decreased markedly with the use of cART but remains to have a poor prognosis.

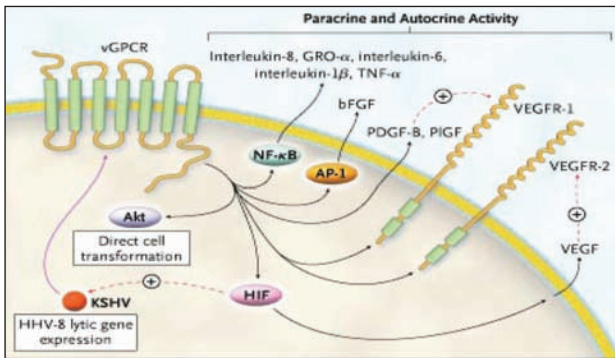


Figure 2. Activities of the vGPCR protein in HHV-8. GRO, growth related protein alpha; TNF, tumor necrosis factor alpha; bFGF, basic fibroblast growth factor; PDGF-B, platelet derived growth factor B; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR-, vascular endothelial growth factor receptors; HIF, hypoxia inducible factor, (originally published in Yarchoan R. Key role for a viral lytic gene in Kaposi's sarcoma. *New England Journal of Medicine* 2006;355:1383. Copyright Massachusetts Medical Society. All rights reserved).

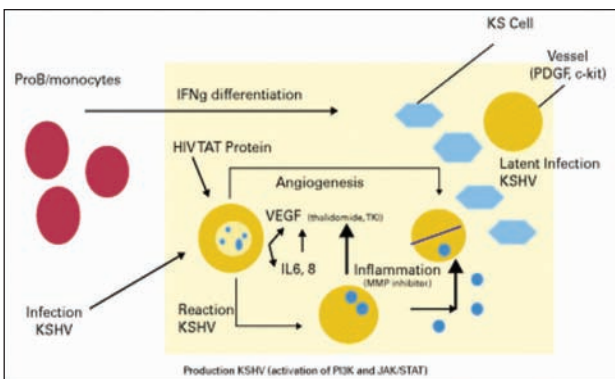


Figure 3. Molecular targeted therapies in AIDS- defining malignancies. ProB, precursor lymphocyte B; KS, Kaposi sarcoma; PDGF, platelet derived growth factor; IFN, interferon; TAT, transactivating protein HIV-tat; KSHV, Kaposi sarcoma associated herpesvirus; VEGF, vascular endothelial growth factor; IL, interleukin; MMP, matrix metalloproteinase, (Spano JD, Costagliola D, Katlama C, et al. AIDS-related malignancies: state of the art and therapeutic challenges. *Journal of Clinical Oncology* 2008;26:4836. Copyright the American Society of Oncology).

Prior to cART, AIDS-associated non-Hodgkin's lymphomas had a poor prognosis and short survival. We described in a retrospective analysis from 1990-93, 11 patients treated with a modified regime (modified m-BACOD) with an overall survival of 8 months (29). 73% of patients were Stage III or IV with extranodal involvement in the gastrointestinal tract, paranasal sinuses or the kidneys. In the post cART era, the prognostic factors are mainly those of the International Prognostic Index (LDH level above normal, stage III or IV, altered performance status of 2 to 4) . Patients were treated with a full dose cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab. The use of hematopoietic growth factors may prevent dose reduction and patients should have prophylaxis against *Pneumocystis jirovecii* while in treatment. cART should continue while in therapy, as control of viral replication has been shown to be independently associated with improved survival (30-33). Recent clinical data has shown risks in the treatment of HIV patients with rituximab, since Kaplan et al from the University of San Francisco described 14% of toxic deaths due to infectious complications with the use of R-CHOP(33). However, Boue et al in a phase -II trial of R-CHOP produced a complete response rate of 77% and 75% two year survival without increasing the risk of opportunistic infections (35). Larger scale studies are necessary to validate this data and even the role of stem -cell transplantation in HIV-infected patients with high risk or relapses of NHL (36-38).

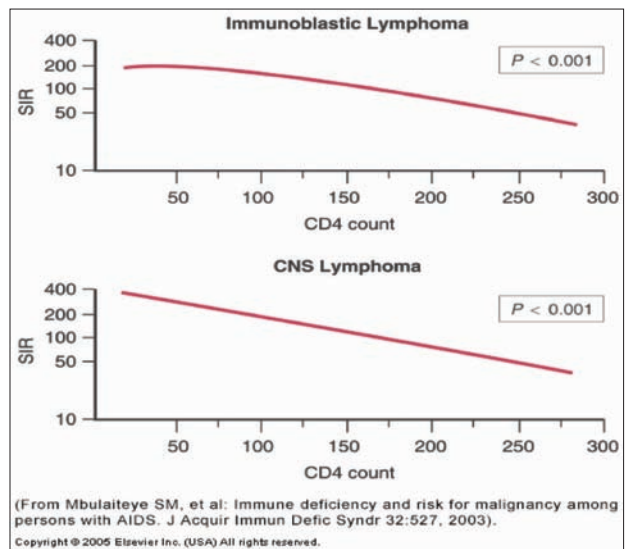


Figure 4. Risk of cancer in persons with AIDS by CD4 count (measured in cells/mm3) at AIDS onset for immunoblastic lymphoma and central nervous system lymphoma presented on a log-transformed scale as the SIR. (From Mbulaiteye SM, et al: Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immun Defic Syndr* 32:527, 2003). Copyright © 2005 Elsevier Inc. (USA) All rights reserved.

Cervical Cancer

Since 1993, the CDC has included cervical cancer as an AIDS-defining malignancy. In a French prospective study of

1124 HIV- infected women, there was an incidence of cervical cancer of 1.1 per 1000 person-years versus 0.14 in the general population (39). Immunosuppression and Human Papilloma Virus (HPV) coinfection play a major role on the pathogenesis of the disease. HPV16, 18, 45 and 31 are commonly associated to invasive cervical cancers; that are usually more aggressive and have a higher recurrence rate. The management is similar to patients from the general population without HIV infection. The use of cART does not seem to have an impact in patient outcome (40). Rigorous cervical cancer screening programs in HIV-infected patients could have an impact in reducing the incidence and mortality rates in the HPV/HIV infection setting.

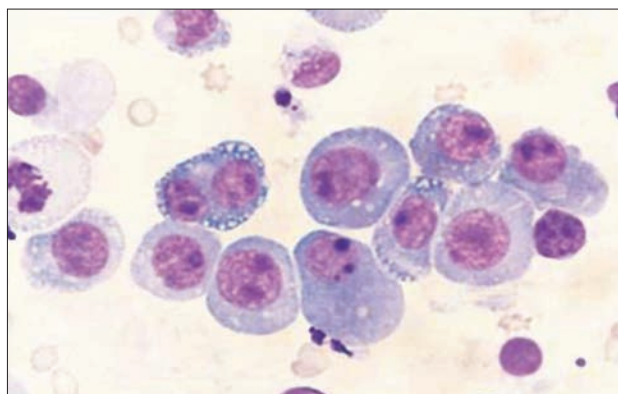


Figure 5. Cytospin preparation of pleural fluid in a patient with primary effusion lymphoma, showing large plasmacytoid tumor (Wright –Giemsa stain X1000) (Jones D. Brief report: primary effusion lymphoma and Kaposi's sarcoma in a cardiac transplant recipient. *New England Journal of Medicine* 1998;339:444-449. Copyright Massachusetts Medical Society. All rights reserved).

Hodgkin's Lymphoma (HL)

Patients with HIV infection have a 5-25 higher risk than the general population of developing HL. It tends to have a more unfavorable histology such as lymphocyte depleted and mixed cellularity and frequently involves the bone marrow and is extranodal (41,42). Epstein-Barr virus has been associated in most cases. Dr. Alexandra Levine has hypothesized the interaction of Reed-Sternberg cells with diverse growth factors in the setting of HIV infection provide proliferation signals for the tumoral cells (Figure 6) (43). Although cART combined with conventional chemotherapy regimens have a positive effect on response and survival, the median survival remains poorer than the general population (44).

Anal cancer

Anal Cancer is also associated to oncogenic types of HPV and its incidence has dramatically increased among HIV patients. In a cross –sectional study, Abramowitz et al showed that 23% of 473 HIV- infected patients had anal HPV- related lesions (36% of homosexual men, 15% of heterosexual men and 11% of

women) (45). Chemoradiotherapy (fluorouracil and mitomycin or cisplatin) produces a similar response to those of the general population, with a 55-75% survival rate and preservation of the sphincter in 60-90% of cases (46). The use of screening techniques such as anal Papanicolaou smear, anoscopy and anal biopsy are necessary to diagnose intraepithelial lesions or true invasive cancers and any person diagnosed with anal squamous cell carcinoma must be evaluated for HIV infection (47).

Lung cancer

Lung cancer has increased its incidence in patients with HIV and is diagnosed at a younger age in mostly smokers (48). Adenocarcinoma remains the most common histology and surgery remains the treatment of choice for localized disease. The disease tends to be advanced on diagnosis, with small series having an overall survival of only 3-8 months (49). As the general population, prevention strategies include tobacco prevention and cessation programs.

Other non-AIDS defining cancers

Basal cell skin cancer, mainly in the trunk, liver cancer, conjunctival cancer (especially in Africa), sarcoma, melanoma, germ cell tumors, myeloma and leukemias have been described in patients with HIV infection. These tend to be more aggressive and have poorer clinical outcomes. Specific therapeutic recommendations are lacking for these new non-opportunistic malignancies.

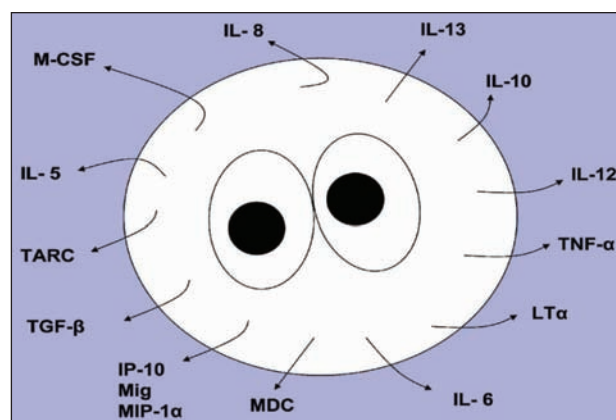


Figure 6. Chemokines and cytokines expressed by the Reed Sternberg cell (Levine AM. Hodgkin lymphoma: to the HAART of the matter. *Blood* 2006;108:3630. Copyright the American Society of Hematology).

cART and chemotherapy interactions

Patients who receive the combination of cancer chemotherapy and cART achieve better response rates than those that receive chemotherapy alone. Drug interactions are high, as protease inhibitors and non-nucleoside reverse transcriptase inhibitors are potent inhibitors or inducers of the cytochrome P450 system

(S0). The coadministration of cART and chemotherapeutic drugs can result in higher drug levels and in decreased efficacy or increased toxicity of one or both classes of drugs. Taxanes have the highest interaction with cART, especially with nelfinavir (S1). cART have no major interaction with anthracyclines. Further research evaluating the safety and pharmacokinetics of antiretrovirals and antineoplastic therapy is necessary.

In conclusion, emerging reports of non-AIDS defining malignancies present a new challenge in the care of patients with HIV infection. Although cART has resulted in a reduction in KS and NHL, that impact has not been seen in non-AIDS defining malignancies. Optimal treatment protocols, similar to those recommended in non-HIV patients should be developed.

Resumen

Desde los primeros informes entre la asociación del Virus de Inmunodeficiencia Humana (VIH) y neoplasia, ha ocurrido un cambio dramático en la incidencia y epidemiología de las malignidades asociadas al SIDA. El Centro para Control de Enfermedades (CDC en sus siglas en inglés) define también a los linfomas Non-Hodgkin y el cáncer cervical como malignidades asociadas al SIDA. Luego del desarrollo de la terapia de combinación altamente activa (cART en sus siglas en inglés), especialmente los inhibidores de proteasa, ha habido un aumento consistente en malignidades no-asociadas al SIDA, tales como el linfoma de Hodgkin, cáncer del pulmón, cáncer hepatocelular, cáncer del ano y otros y una disminución en las neoplasias asociadas al SIDA. Aunque el aumento en tumores no-asociados al SIDA puede ser el resultado de una mayor sobrevivencia en estos pacientes, otros factores como hábitos tóxicos (abuso del alcohol) y co-infección con virus tales como hepatitis B y C y el virus de papiloma humano pueden tener un rol importante. Las interacciones de la terapia de combinación altamente activa y una reconstitución inmune incompleta pueden ser otros factores que expliquen este aumento en cánceres no-asociados al SIDA. Estos informes emergentes de malignidades no-asociadas al SIDA presentan un nuevo reto en el cuidado de los pacientes infectados con el VIH y requiere protocolos de tratamiento que tomen en consideración la interacción entre la terapia CART y la quimioterapia sistémica. Presentaremos el estado actual de las malignidades relacionadas al SIDA, su patofisiología, epidemiología y manejo con énfasis en los patrones cambiantes de presentación.

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