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Cancer Biomarkers in HIV Patients

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Abstract

Purpose of review—In this review, we update investigations related to cancer biomarkers in HIV-infected populations

Recent findings—CD4 lymphocyte is associated with PCNSL, systemic NHL (except perhaps for BL), KS, cervical cancer and anal cancer. HIV load is associated with BL and systemic NHL (but not PCNSL), with KS and with anal cancer. CD40 ligand incorporated into the HIV envelope and expression of activation induced cytidine deaminase may help explain the relationship between HIV load and BL. Genetic polymorphisms have been identified that are linked to lymphoma in HIV patients. B cell activation as manifest in immunoglobulin light chain production may be an important marker for NHL risk. Cytokines and related molecules (IL10, sCD30) may identify patients at high risk for NHL. EBV in CSF is useful as a marker for PCNSL, although with the falling incidence of PCNSL, the specificity of the test has been called into question. EBV and KSHV have not yet emerged as especially promising markers of risk for either lymphoma or KS.

Summary—CD4 lymphocyte count, HIV load, germ line genetic polymorphisms, cytokine and related molecules and immunoglobulin light chains all show increasing promise as biomarkers of malignancy in HIV patients.

Keywords

Lymphoma; Hodgkin's; Kaposi's sarcoma; cervical cancer; HIV

Introduction

Malignancies with an increased incidence in HIV patients include the AIDS-defining malignancies (PCNSL, systemic BL and DLBCL, KS, cervical cancer) and other NADC. Cancers of the anus, cervix, or pharynx, penis, and vagina or vulva are all HPV-associated and risks of these cancers are all higher among persons with AIDS as detailed in a recent analysis linking US AIDS and Cancer registries [1]**. The SIR's for the association of some of these malignancies with HIV infection, such as invasive anal cancer (SIR of 34.6, CI 95% 30.8–38.8), are quite striking, while others, such as oropharyngeal cancer, show a much more modest increase in risk (SIR 1.6, CI 95% 1.2 to 2.1). NADC EBV-related cancers (lymphoid and epithelial) are also increased, including HL (SIR 11, CI 8.8 to 15) and nasopharyngeal cancer (SIR 4.1, CI 95% 2.1 to 7.9) [2]**. Lung cancer is increased in HIV populations (SIR 2.6, CI 95% 2.1 to 3.1), although the salient features of the association remain uncertain. Evidence has been presented that lung cancer risk is increased independent of smoking behaviors [3], but a recent report from the WIHS indicates that incidence rates of lung cancer were similar among HIV-infected and uninfected women and did not differ by HIV status, leading the investigators to conclude that HIV infection is

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strongly associated with smoking behaviors that increase lung cancer risk [4]*. Biomarkers that have been investigated for these cancers in HIV-infected patients include cellular biomarkers (CD4 lymphocyte count), proteins of various sorts in plasma or serum (cytokines, receptor-derived proteins, immunoglobulins), viral nucleic acids (HIV, EBV, KSHV), and germ line polymorphisms in a variety of genes. Those addressed in this review are summarized in Table 1.

CD4 lymphocyte count and HIV load

The CD4 lymphocyte count was among the first biomarkers of immunodeficiency associated with HIV infection and is certainly the best studied. HIV load measurements provide additional information. Recent studies have investigated the character of the association of these markers with malignancies and have shown that the risks are not uniform but are associated with particular malignancies. The associations with CD4 lymphocyte count and HIV in some instances are orthogonal rather than parallel and these features may provide insights into aspects of pathogenesis and prevention.

Early studies suggested that nadir CD4 lymphocyte count was an important predictor of AIDS-related lymphoma [5,6]. In 2007, investigators at the NCI reported data from AIDS and Cancer Match Registries confirming an association of CD4 lymphocyte count at AIDS onset with AIDS NHL [7]. The hazard ratio varied as a function of the type of lymphoma. For PCNSL, the HR was 1.85 for each decline of 50 CD4 cells per microliter, whereas for systemic NHL it was 1.09. Among systemic NHL, there was further variation. DLBCL was associated with an HR of 1.12 for each decline of 50 CD4 cells whereas BL showed no association with CD4 lymphocyte count. The relationship of AIDS NHL to CD4 lymphocyte count was readdressed in 2009 by the UK Collaborative HIV Cohort [8]*. They reported that the most recent CD4 lymphocyte count rather than the nadir lymphocyte count was predictive of AIDS NHL. A multivariable analysis from the Clinical Surveillance Study in Germany also reported in 2009 yielded a similar result [9]**. Only the most recent CD4 lymphocyte count and not the nadir CD4 lymphocyte count was independently associated with risk of developing lymphoma (<200 HR 8.16, 201–350 HR 5.21). As in earlier studies, the association of NHL with CD4 count was a function of lymphoma type. These investigators grouped lymphoma diagnoses into four categories: Burkitt and Burkitt-like, “high grade” non-Burkitt B cell lymphoma (diffuse large B cell lymphoma and primary effusion lymphoma), lymphoma not otherwise specified, and PCNSL. CD4 T cell counts ≤350 cells/mcL were associated with risk of non-Burkitt aggressive systemic lymphoma. A more granular perspective with regard to PCNSL was offered by a small study indicating that HIV patients who develop PCNSL lack CD4 lymphocytes targeting EBV, irrespective of the patient’s absolute CD4 lymphocyte counts [10].

Viremia was also a predictor of AIDS lymphoma. In the German study cited above, cumulative HIV viremia, rather than the latest viral load, best predicted the development of lymphoma [9]**. Associations with sustained viremia over time differed as a function of pathologic subtype. Cumulative HIV viremia was a risk factor for Burkitt-type and non-Burkitt-type AIDS-related lymphoma but not for PCNSL. And in a retrospective study from Baltimore, investigators found that NHL risk was independently associated with both current CD4 lymphocyte count and time spent with a viral load above 100,000 copies/mL [11]**.

Why might viremia be related to NHL risk independently of CD4 lymphocyte count? One possible explanation comes from the discovery of a potent activator of immunoglobulin heavy-chain gene class switch recombination and somatic hypermutation incorporated into the HIV envelope [12]**. The envelope of HIV from PBMC includes host cell CD40 ligand,

a potent B cell stimulatory molecule that is a member of the TNF super family. CD40 ligand induces the expression of activation induced cytidine deaminase, the enzyme that plays a crucial role in processes that generate immunoglobulin diversity, but that also is believed to be central to the pathogenesis of most NHL, acting to induce lymphomagenic DNA lesions, such as oncogene mutations and translocations. HIV virions that carry CD40 ligand may stimulate polyclonal B cell activation characteristic of HIV infection (see below) and generate the molecular lesions that contribute to the development of NHL in a process that is independent of the CD4 lymphocyte count, but which would be expected to be dependent on cumulative exposure to HIV.

The relationship of HL with CD4 lymphocyte count has been a focus of interest. In 2006, NCI investigators reported data from US cancer and HIV match registries indicating that the incidence of HL in patients with CD4 lymphocyte counts <50/mcL was less than the incidence in patients with CD4 lymphocyte counts 150 – 199/L [13]. The authors suggested that HL incidence is greatest with moderate immunosuppression and that improvements in CD4 lymphocyte counts resulting from combination antiretroviral therapy might explain an apparent increase in HL in HIV patients. In a study of non-AIDS defining cancers in HIV patients (the Chelsea and Westminster HIV cohort, predominantly men) HL was also not associated with CD4 lymphocyte counts [14]. In 2009, Swiss HIV Cohort Study investigators reported that they were unable to demonstrate increased HL risk in the setting of improved immunity [15]*. They noted a tendency for increased risk with declining CD4 counts that did not achieve significance and a lower CD4/CD8 ratio 1 to 2 years before HL diagnosis. In a letter, Dolcetti and colleagues called attention to the hypothesis that in immunocompetent HL patients, lymphocytopenia may reflect sequestration of lymphocytes at tumor sites*[16]. If this phenomenon also occurred in HIV HL patients, then the number of circulating CD4 lymphocytes close to the time of HL diagnosis might reflect lymphocyte redistribution, as well as immune competence or reconstitution. The Swiss investigators reanalyzed their data to assess the utility of declines in lymphocyte counts to predict future HL development, finding a drop in the year preceding HL diagnosis, consistent with lymphocytopenia developing as a consequence of the tumor*[17]. Clearly further work is needed, but the dynamics of lymphocyte changes in HIV patients with HL may be especially complex.

Many studies have linked CD4 lymphocyte count and the risk of KS. A recent collaborative report from 25 cohorts from Europe, Australia, Canada, and sub-Saharan Africa specifically examined patients developing KS after starting combination antiretroviral therapy [18]. In this study of homosexual men, CD4 count was associated with KS, but duration of HIV infection, age, or nadir CD4 lymphocyte count were not independently associated with KS. Similarly, a recent French study indicated that current CD4 lymphocyte count was the best predictor but also noted that KS increased with current plasma HIV RNA greater than 100,000 copies per mL compared to patients with controlled viral load [19].

In the US AIDS and cancer match registries study noted above, a low CD4 lymphocyte count was associated with an increased risk of invasive cancer of the anus in men** [1]. There was a trend toward increased risk of invasive cervical cancer among women but this did not achieve statistical significance. This association with CD4 cell count differed from previous observations in the era before combination anti-retroviral therapy and the investigators hypothesized that high mortality among individuals with a low CD4 lymphocyte counts, before the availability of effective antiretroviral therapy, may have masked an association between immunosuppression and the risk of invasive cancer. Improvements in survival accompanying combination antiretroviral therapy allows time for progression to invasive cancers. In a report from France cervical cancer was strongly associated with current CD4 lymphocyte count whereas anal cancer increased with the time

during which the CD4 lymphocyte count was less than 200 cells per μL and viral load was greater than 100 000 copies per mL [19].

Genetic polymorphisms, HIV progression, and cancer

Genetic polymorphisms associated with many cancers in the general population have received considerable attention in recent years. Especially relevant to the discussion of HIV associated cancers are findings regarding genetic susceptibility to lymphoma. In general populations, the past two years has seen confirmations of a role for polymorphisms in the tumor necrosis factor (TNF) and interleukin-10 (IL10) gene [20–22].

With regard to HIV and cancer, the first genetic polymorphisms studied were those that conferred resistance to HIV itself. Two genetic polymorphisms identified as slowing HIV progression have been studied with regards to AIDS-defining cancers. Homozygotes for CCR5delta32, a deletion that blocks expression of the CCR5 co-receptor used in HIV entry, are protected against HIV infection, and HIV infected heterozygotes show slow HIV disease progression. Early studies showed that HIV-infected CCR5delta32 heterozygotes are less likely to develop AIDS NHL than others [23]. The original reports suggested that these effects were independent of general disease progression and persisted even when CD4 lymphocyte count and duration of HIV disease were controlled for. The inference that CCR5 might be important specifically in lymphoma pathogenesis and not merely in HIV disease progression was supported by the observation that CCR5delta32 heterozygotes were not protected from KS. Also, these investigators demonstrated that RANTES could promote B cell activation via its interaction with CCR5, and suggested that those who were CCR5delta32 heterozygotes might be resistant to chronic B cell activation induced by CCR5 ligands. A second polymorphism also slows HIV disease progression although it does not confer resistance to lymphomagenesis [24]. Other polymorphisms not implicated in the general progression of HIV disease have been identified as affecting the risk of ARL. Thus a CXCL12 (SDF-1) variant allele is associated with increased risk of AIDS NHL [24]. IL10 polymorphisms that are associated with increased *IL10* expression also have been associated with AIDS NHL [25].

Two recent studies are relevant to consideration of the cancer specific relevance of these genetic markers. Pooled data from NHL studies excluding HIV patients suggests that CCR5delta32 may be associated with decreased risk of diffuse large B cell lymphoma and follicular lymphoma [26]**. Interestingly, the effect was limited to men. Neither the CCR2 64I nor the CXCL12 (SDF-1) variant allele were associated with increased risk in these non-HIV populations. Thus it is possible that identification of protective polymorphisms in HIV patients has also led to identification of a protective marker in the general population. It should be noted that the investigators were appropriately cautious in reporting their conclusion and that further studies will be required to substantiate the finding. A new report published in 2010 reinforces the importance of IL10 [27]**. IL10 alleles linked to lower IL10 production and lower circulating IL10 levels were associated with decreased risk of PCNSL.

Genetic studies have also been reported in cervical cancer in HIV infected patients. CCR2 64I, the polymorphism that protected against HIV progression but not against lymphoma, has been reported to be protective against cervical cancer in HIV patients [28]. However, a recent investigation carried out in black South Africans suggested the polymorphism to be associated with an increased risk of cervical cancer [29]. Although the study included HIV patients, the great majority of patients were not HIV infected. Whether the discrepancy between studies reflects different populations (HIV-infected versus predominantly uninfected African) or other factors remains to be determined.

A fourth study focused on SNPs in the genes encoding lymphotoxin alpha (LTA) and tumor necrosis factor (TNF) which had been previously linked with non-Hodgkin lymphoma in the general population [30]**. Although SNPs in these 2 genes have been repeatedly associated with NHL, the investigators noted that these genes most often occur on one of the most conserved extended haplotypes in the human genome with extraordinary allelic invariance across several megabases. Their results corroborated an overall haplotypic effect of this conserved extended haplotype on NHL pathogenesis. This conserved extended haplotype has not been associated with HIV-related KS in previous studies. The analysis supports an association with one or more genetic variants somewhere in the conserved extended haplotype region rather than suggesting a particular gene specific causal relationship.

B Cell Activation and lymphoma

Interest in immune stimulation or activation as a contributor to malignancy, particularly lymphoid malignancy, has increased in recent years. B cell activation begins early after HIV infection and is manifest by polyclonal hypergammaglobulinemia and phenotypic changes in circulating B cells. Before the era of combination antiretroviral therapy high levels of serum globulins were reported to be predictive of AIDS NHL [31]. In the recent Baltimore study, although serum globulin levels were elevated in HIV+ subjects when compared with the general population, NHL risk was unrelated to this marker [11]*. Nonetheless, assays of B cell immune activation are among the most promising new biomarkers. A systematic approach was taken to investigate serum immunoglobulin proteins including serum protein electrophoresis, immunofixation and assays for kappa and lambda light chains in three cohorts of HIV-infected patients [32]**. The cohorts were of gay men in Washington and New York (Gay Men's Study), the Multicenter Hemophilia Study and the AIDS Cancer Cohort Study. In aggregate 5000 HIV infected individuals were studied. Among these patients were 66 patients diagnosed with non-Hodgkin's lymphoma with blood specimens available before diagnosis. These were compared with controls with similar demographics and blood sample availability. Most were not receiving highly active antiretroviral therapy. Although patients and controls had higher IgG levels than the general population, immunoglobulin levels did not differ between patients and controls. In contrast, patients had higher levels of kappa and lambda free light chains 0–2 years and 2–5 years before diagnosis (and levels were also higher than that observed in the general population) (Fig. 1). Differences were most apparent in individuals with CD4 lymphocyte counts greater than 100 cells/mcL. Among those with less than 100 CD4/mcL counts, the presence of an association with free light chains was only apparent 2–5 years before diagnosis rather than in the 0–2 years before diagnosis. Among controls there was an inverse correlation with CD4 lymphocyte counts. Interestingly, levels of IgG, IgA, and IgM were not associated with NHL risk. Neither MGUS nor abnormal free light chain ratios predicted lymphoma, and both markers of B cell clonality occurred with equal frequency in cases and controls. Thus markers of polyclonal B cell activation but not clonal activation were suggested to be important.

Cytokines and lymphoma

As noted above NHL risk is related to genetic variation in genes encoding cytokines that modulate the inflammatory process or that are associated with B cell activation. Studies of cytokines among HIV patients were among the earliest to document cytokine levels associated with lymphoma risk [25,33,34]. Soluble CD30 was identified in prediagnostic serum of patients with increased risk of developing AIDS-related NHL [35]. This observation led to a subsequent study to investigate whether in the general population serum sCD30 was associated with NHL risk [36]*. In a recent nested studies in the Multi center AIDS Cohort Study, we found that elevated serum levels of B cell stimulatory factors,

including IL6, IL10, CXCL13 and TNF alpha, were associated with increased risk for the development of NHL in HIV+ persons (unpublished observations). In these studies, this association was seen as early as five years before NHL diagnosis.

EBV and KSHV DNA and body fluids

EBV is associated with approximately half of all AIDS-related lymphomas and with virtually all cases of PCNSL and HL. Detection of EBV DNA in CSF has been a standard for many years for confirmation of the diagnosis of PCNSL in the setting of suggestive radiographic findings but in the absence of biopsy [37]. The specificity has been questioned, and this diminished specificity may reflect the declining incidence of the disease. Quantitation, rather than qualitative measurement, has been reported to increase specificity [38]. A study from Argentina reported that EBV DNA in PBMCs was not useful for diagnosing PCNSL [39] and other studies have failed to show much utility for the assessment of PBMC EBV in the detection of systemic lymphoma [40]. A recent survey of EBV DNA detection in whole blood from various clinical laboratories in France reported a correlation between EBV DNA and CD4 lymphocyte count in HIV patients [41].

KSHV DNA in lymphocytes and in plasma or serum, and humoral responses to KSHV, are established as markers of KSHV infection, and as such there is general recognition that the presence of these indicators of infection identifies subjects more likely to develop KS or KSHV-associated lymphoma, than those without these markers. But little more has been done with regard to their prognostic significance. The AIDS Malignancy Consortium published a report indicating that among individuals with viral DNA in PBMC or plasma, the viral copy number did not differ between patients with lymphoma and patients with KS (i.e. viral DNA indicated infection, but among those infected, the level of DNA did not differentiate those with or without virus-associated disease) [42]*. Nonetheless, KSHV DNA in plasma may be measuring something important with regards to treatment outcome. In a study of the treatment of AIDS-KS, KSHV DNA level in plasma prior to treatment identified patients at higher risk for death or failure of tumor to respond to therapy, or could be useful in identifying patients who would benefit from earlier institution of combination antiretroviral therapy [43]*.

HPV

HPV-16 integration in the cells that make up anal lesions has been offered as a potential biomarker for lesions at high risk for malignancy [44]. HPV integration is thought to be important in the pathogenesis of HPV related cervical cancer but has not been much studied in the context of anal cancer. Investigators in Spain showed that overall anal HPV-infection prevalence in HIV+ subjects was 78%, that 29% had HPV-16 infection, and 9% showed HPV-16 integration. In a multivariate analysis, HPV-16 integration was the most important risk factor for cytologic abnormalities.

Conclusion

Early detection/prevention strategies have not been established as useful in lymphoma or KS. However, the situation may be changing. Thus in hematopoietic stem cell and organ transplantation, there is increased risk of EBV-driven lymphoproliferative disease prophylactic or “pre-emptive” therapy (when EBV monitoring indicates a rising EBV load) with an antibody that targets B cells has sometimes been instituted [45]*. If HIV patients at very high risk might be similarly identified, such an intervention might be warranted.

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Abbreviations

ARL	AIDS-related lymphoma
BL	Burkitt's lymphoma
CI 95%	confidence interval 95%
EBV	Epstein-Barr virus
HL	Hodgkin lymphoma
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus (HHV-8)
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NADC	Non-AIDS defining cancer
PCNSL	primary central nervous system lymphoma
SIR's	standardized incidence ratios
SNP	single nucleotide polymorphism
WIHS	Women's Interagency HIV Study

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Papers of particular interest, published within the ...period of review have been highlighted as:

*of special interest

**of outstanding interest

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Fig 1.

Non-Hodgson's lymphoma (NHL) risk as a function of serum free light chain (FLC) levels among HIV-infected people. Odds ratios (ORs) and associated 95% CIs are presented for NHL in relation to FLC levels. FLC levels are categorized as normal or as a multiple of the upper limit of normal (ULN). ULNs are 1.94 mg/dL for κ and 2.63 mg/dL for λ . The panels correspond to results for (A) κ FLC levels measured 0 to 2 years prior to NHL diagnosis/control selection; (B) κ FLC levels measured 2 to 5 years prior to NHL diagnosis/control selection; (C) λ FLC levels measured 0 to 2 years prior to NHL diagnosis/control selection; and (D) λ FLC levels measured 2 to 5 years prior to NHL diagnosis/control selection.

Table 1

<u>Tissue</u>	<u>Biomarker</u>	<u>Cancers</u>			
Cells	CD4	PCNSL	Systemic NHL (non-BL)	?HL	Anal Ca
					KS
Nucleic acids in blood (serum, plasma, PBMC)	HIV load		Systemic NHL	BL	
DNA in plasma, serum, PBMC	EBV				
	KSHV				KS
DNA in CSF	EBV	PCNSL			
Germline DNA	Genotype: CCR5delta32		Systemic NHL		
	Genotype: CCR2 64II				? Cervical Ca
Proteins including cytokines and related molecules in plasma or serum	Ig light chains in serum		Systemic NHL		
	sCD30		Systemic NHL		
	IL10		Systemic NHL		