Serum Soluble CD23 Level Correlates with Subsequent Development of AIDS-related Non-Hodgkin’s Lymphoma

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Abstract

The cytokine soluble CD23 (sCD23) has been shown to act as a B cell growth factor and to be elevated in serum prior to development of AIDS-related non-Hodgkin’s lymphoma (AIDS NHL). To further characterize the elevation of serum sCD23 in AIDS NHL patients and investigate its potential as a diagnostic test, a matched case-control study of AIDS NHL (n = 101) was nested within the Multicenter AIDS Cohort Study. Serum sCD23 was measured in cases’ and controls’ serum specimens at three different time periods (0 – 6, 6 – 12, and 12 – 18 months) and CD4+ thresholds (0 – 99, 100 – 199, and 200 – 299 cells/μl) prior to the case’s NHL diagnosis. Changes in serum sCD23 over time were examined in AIDS NHL cases relative to controls, and t tests were performed to determine whether cases’ serum sCD23 exceeded that of controls at each time period and CD4+ threshold.

Overall, cases’ median serum sCD23 levels were approximately double those of controls. Serum sCD23 concentration was positively correlated with lymphocyte counts for both cases and controls. The difference in cases’ and controls’ serum sCD23 levels became greater as AIDS NHL diagnosis date approached: in the 18 months preceding the case’s NHL diagnosis, serum sCD23 was stable in cases but dropped in controls. Although this difference was statistically significant (P < 0.05), it was not clinically significant. It is unlikely that serum sCD23 would make a useful test for AIDS NHL because the magnitude of the difference between cases and controls was small and there was no change in serum sCD23 in cases that would indicate disease.

Introduction

NHL1 is the second most common malignancy associated with AIDS, affecting an estimated 4 – 10% of AIDS patients (1). In the MACS, the incidence has risen 21% per year since 1985 (2), the year the United States Centers for Disease Control and Prevention added NHL as an AIDS-defining condition. Like most NHL in the Western Hemisphere, AIDS-related NHL is almost entirely derived from B cells (3). NHL in AIDS patients is different from non-AIDS NHL in that it is more aggressive and has a poorer prognosis, frequently being an advanced-stage tumor with extranodal involvement at diagnosis (4). Unlike non-AIDS NHL, AIDS NHL is predominantly diffuse large cell/immunoblastic lymphoma or diffuse SNCCL in appearance (5). This cancer can be difficult to diagnose, because most of the clinical symptoms of lymphoma (e.g., enlarged lymph nodes, fatigue, weight loss, and night sweats) can also be the result of HIV infection or HIV-related opportunistic infections and are thus nonspecific to AIDS NHL (6).

Much remains unknown regarding the etiology and pathogenesis of AIDS NHL. Epidemiological studies have elucidated few extrinsic risk factors for this disease (7). AIDS NHL often occurs later in the course of HIV infection than many other AIDS-defining conditions (8); large cell/immunoblastic lymphomas are typically diagnosed at a more immunocompromised state than is SNCCL (9). The EBV is believed to be a likely causative agent of AIDS NHL because it is capable of transforming B cells to malignancy and has been consistently found in AIDS NHL tumor tissue. Reports vary, but EBV is found in roughly half of all systemic AIDS NHL (10) and virtually all AIDS PCNSL (11).

The c-myc, ras, and bcl-6 oncogenes and p53 tumor suppressor gene have also been associated with AIDS NHL (5). These genes and EBV are not distributed randomly across AIDS NHL cases, but rather tend to be correlated with particular histological subtypes. c-myc oncogene activation and p53 tumor suppressor gene inactivation are both associated with SNCCL and are correlated with each other (10). Activation of

1 The abbreviations used are: NHL, non-Hodgkin’s lymphoma; AIDS NHL, AIDS-related NHL; MACS, Multicenter AIDS Cohort Study; sCD23, soluble CD23; SNCCL, small noncleaved cell lymphoma; B-CLL, B cell chronic lymphocytic leukemia.
Serum sCD23 and Subsequent AIDS NHL

ras oncogene is also associated with SNCCL (10). In contrast, EBV appears to be associated with large cell immunoblastic NHL and is found in only a small portion of SNCCL (10).

Although few extrinsic factors have been determined to influence AIDS NHL risk, intrinsic immunological characteristics may in part explain AIDS NHL etiology. Yawetz et al. (12) found levels of sCD23 and IgE in serum to be significantly elevated prior to AIDS NHL diagnosis in a subset of the MACS cohort. The CD23 molecule is a single-chain 45-kDa transmembrane glycoprotein, found on most resting mature B cells, that acts as a low-affinity IgE receptor. Its expression is induced by IL-4, IL-13, and EBV infection. CD23 is cleaved into soluble fragments, known as sCD23, that are released into the extracellular fluid (13). There is accumulating evidence that sCD23 serves as a B cell growth factor (13), so it is plausible that sCD23 contributes to the development of B-cell NHL as well as being a likely preclinical marker. Elevated levels of serum sCD23 have been found in patients with B-CLL, hairy cell leukemia, and non-metastatic nasopharyngeal carcinoma (13). Serum sCD23 has been shown to be a useful marker for diagnosis and monitoring of B-CLL patients (14, 15) and for predicting prognosis of nonmetastatic nasopharyngeal carcinoma patients (16) and low-grade NHL patients (17).

The goals of this study were to characterize and compare levels of serum sCD23 and IgE in AIDS NHL cases and matched AIDS controls at various CD4+ T cell counts and time points prior to lymphoma diagnosis. A difference in the magnitude and patterns of serum sCD23 and/or IgE in AIDS NHL patients could shed light on the pathogenetic mechanisms that lead to AIDS NHL and may also lead to the development of a helpful diagnostic test for this disease.

Patients and Methods

Patient Population. This case-control study was nested within the MACS, a prospective study of the natural history of HIV infection and AIDS described in detail elsewhere (18). The MACS cohort consists of adult homosexual and bisexual men who were enrolled at four metropolitan areas (Baltimore, Chicago, Los Angeles, and Pittsburgh) in 1984–1985 and 1987–1991 and who are seen semiannually for a physical examination and interview. Blood is collected for both laboratory testing and for storage of serum and plasma at −70°C and cells at −135°C in repositories for future research. AIDS-related clinical outcomes are ascertained from self-reports and by other surveillance, with medical record review to confirm diagnoses. There are 5579 MACS participants altogether, 1590 of whom had been diagnosed with AIDS and 167 of whom had been diagnosed with AIDS-related lymphoma (109 systemic NHL and 58 PCNSL) as of June 1997. This study used data prospectively collected from the participants at their follow-up visits as well as data generated by testing frozen serum specimens.

Cases were all individuals with an AIDS NHL diagnosis and a serum specimen available from at least one of the three time points or CD4+ thresholds of interest (described below) and were able to be matched to a control; the AIDS NHL diagnosis may or may not have been the initial AIDS-defining diagnosis. One control was selected for each case, matched on AIDS diagnosis date (±1 year) and CD4+ lymphocyte percentage (±15%) at the visit closest to the AIDS diagnosis date (before or after). Among the possible controls for each case, the one with the minimum difference in CD4+ lymphocyte percentage was chosen. These matching criteria were used to select controls whose risk of developing NHL was similar to that of their corresponding cases, controlling for the degree of immunosuppression and secular trends in diagnosis and treatment of HIV infection and AIDS. Controls were required to be alive at the time of the case’s NHL diagnosis, have no history of leukemia or lymphoma, and have a serum specimen available from at least one of the three time points or CD4+ thresholds of interest.

Sampling Scheme. One serum specimen was selected for each study participant at each of the following time points or CD4+ thresholds prior to the case’s NHL diagnosis date: (a) less than 6 months; (b) at least 6 months but less than 12 months; (c) at least 12 months but less than 18 months; (d) the first time the CD4+ T cell count fell within the 200–299 cells/μl range; (e) the first time the CD4+ T cell count fell within the 100–199 cells/μl range; and (f) the first time the CD4+ T cell count fell within the 0–99 cells/μl range. One serum specimen could meet the requirements of both a time point and CD4+ threshold.

Fig. 1 is a schematic diagram of the samples taken for a hypothetical case/control pair. S, serum sample point; 1, <6 months; 2, ≥6 months but <12 months; 3, ≥12 months but <18 months; 4, first-time CD4 in the range of 0–99 cells/μl; 5, first-time CD4 in the range of 100–199 cells/μl; 6, first-time CD4 in the range of 200–299 cells/μl. All samples were taken prior to the case’s lymphoma diagnosis.

![Fig. 1. Schematic diagram for the study sampling scheme showing sample points for a hypothetical case/control pair. S, serum sample point; 1, <6 months; 2, ≥6 months but <12 months; 3, ≥12 months but <18 months; 4, first-time CD4 in the range of 0–99 cells/μl; 5, first-time CD4 in the range of 100–199 cells/μl; 6, first-time CD4 in the range of 200–299 cells/μl. All samples were taken prior to the case’s lymphoma diagnosis.](image)
the amounts of sCD23 measured in these control specimens were plotted over time to determine interplate variation. All specimens, controls, and standards were run in duplicate to ascertain assay variability. The quality of each run was determined by examining the standard curve, amounts measured in the manufacturer and positive patient controls, and the coefficients of variation of specimens, controls, and standards run in duplicate to ascertain assay variability. The test was used according to the manufacturer’s instructions except that the number of washes was increased from three to five to increase assay precision. The tests were run at the Johns Hopkins School of Hygiene and Public Health.

**IgE Measurements.** IgE was measured in every serum sample using the FlipSCREEN Total IgE ELISA from ALerCHECK, Inc. (Portland, ME). This assay detects IgE at levels as low as 5 IU/ml. A positive control specimen provided by the assay manufacturer was run on each plate; the amount measured in the positive control had to fall within a specified range or the specimen on that plate were rerun. Any samples above the range of the standard curve were diluted and reanalyzed. All specimens, controls, and standards were run in duplicate to ascertain assay variability. The test was used according to the manufacturer’s instructions except that the sample incubation time was increased from 1 to 3 h because this increased sensitivity for low samples and decreased overall variability. The assays were run at the University of California at Los Angeles School of Medicine.

**Interview and Physical Examination Data.** This study used interview and clinical data collected in the MACS. Previously reported risk factors for AIDS NHL and for elevated serum sCD23 levels were examined: age; race; educational level; body mass index; alcohol and tobacco consumption; history of allergies, asthma, autoimmune disease, or infectious mononucleosis; history of radiation therapy, transfusions, aspirin, immunosuppressive drugs, or steroids; CD4+ T cell count; HIV-1 viral load; and AIDS-related symptoms, such as persistent bruising, diarrhea, fatigue, fever, swollen glands, headache, rash, night sweats, thrush, or unexpected weight loss. These data from the baseline visit, as well as for the visits corresponding to the serum sCD23 measurements, were used in analyses.

**Statistical Analysis.** To test the hypotheses that levels of serum sCD23 and IgE prior to diagnosis in AIDS NHL cases exceeded those in controls, paired t tests were performed at each of the three time points and three CD4+ thresholds. The natural logarithm transformation was used on sCD23 and IgE to normalize their distributions. To determine whether the relationship between serum sCD23 and AIDS NHL case status still held after accounting for other factors related to AIDS NHL risk and serum sCD23 level, a multivariate conditional logistic regression model, having log(odds of case status) as the dependent variable and serum sCD23 and other risk factors for AIDS NHL and elevated sCD23 as independent variables, was fit for each time point and CD4+ threshold. Nonparametric Spearman’s correlations were used to study associations between sCD23 and lymphocyte counts at the visit closest to the case’s AIDS NHL diagnosis.

**Human Subjects.** This study was approved by the Johns Hopkins University School of Hygiene and Public Health Committee on Human Research; the MACS has been approved by the local institutional review boards at Johns Hopkins University, Northwestern University, University of Pittsburgh, and the University of California at Los Angeles.

### Results

**Study Subjects.** Of the 167 AIDS NHL cases diagnosed in MACS participants, 29 were excluded because they had no available serum samples at any of the time points or CD4+ thresholds of interest, and 37 were excluded because there were no controls that met the matching criteria. One hundred one cases were matched to controls according to the criteria described above; 24% were immunoblastic lymphomas, 18% were large cell lymphomas, 15% were SNCCls, and 7% had other identifiable histology. For the remaining 36%, histological subtype could not be determined from the patient’s medical records. The 101 cases who were matched to controls were compared to the 66 cases who were not matched to controls with respect to AIDS diagnosis date, NHL diagnosis date, NHL survival time, age at NHL diagnosis, race, center, proportion of PCNS lymphomas, and whether or not NHL was the presenting AIDS diagnosis. Differences were small and not statistically significant (data not shown).

AIDS NHL cases were similar to their matched controls with respect to center of enrollment, age at enrollment, race, educational level, CD4+ T cell count, and HIV-1 viral load measurements made at baseline, and CD4+ T cell count/percentage point at AIDS diagnosis date (Table 1). The difference in AIDS diagnosis dates was statistically significant but not clinically meaningful, being only 3 months. Although the controls were permitted to have a CD4+ T cell percent within 15 percentage points of the case’s, 90% of controls had a CD4 percent within 6 percentage points of that of their case because the closest match of all eligible matches was selected. The four most common presenting AIDS diagnoses in cases were, in order, systemic NHL (n = 33), Pneumocystis carinii pneumonia (n = 18), Kaposi’s sarcoma (n = 10), and primary CNS lymphoma (n = 9). In controls, P. carinii pneumonia (n = 27), Kaposi’s sarcoma (n = 25), Candida infection (n = 8), and

### Table 1 Comparison of AIDS NHL cases and matched AIDS controls in the MACS with respect to demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Case Characteristics</th>
<th>Cases (n = 101)</th>
<th>Controls (n = 101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltimore</td>
<td>26%</td>
<td>26%</td>
<td>0.54a</td>
</tr>
<tr>
<td>Chicago</td>
<td>22%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>12%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Los Angeles</td>
<td>40%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Median age at enrollment (yr)</td>
<td>34</td>
<td>34</td>
<td>0.23b</td>
</tr>
<tr>
<td>Race (white non-Hispanic)</td>
<td>84%</td>
<td>79%</td>
<td>0.36c</td>
</tr>
<tr>
<td>Education (college degree)</td>
<td>50%</td>
<td>53%</td>
<td>0.57d</td>
</tr>
<tr>
<td>Median CD4+ T cell count at baseline (cells/μl)</td>
<td>547</td>
<td>504</td>
<td>0.59e</td>
</tr>
<tr>
<td>Median HIV-1 viral load at baseline (copies/ml)</td>
<td>35,751</td>
<td>38,412</td>
<td>0.90f</td>
</tr>
<tr>
<td>Median AIDS diagnosis date</td>
<td>August 1990</td>
<td>November 1990</td>
<td>0.01b</td>
</tr>
<tr>
<td>Median CD4+ T cell count at AIDS diagnosis date (cells/μl)</td>
<td>120</td>
<td>89</td>
<td>0.80g</td>
</tr>
<tr>
<td>Most common presenting AIDS diagnosesa</td>
<td>34% NHL 28% PCP N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19% PCP 26% KS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10% KS 8% Candida</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9% PCNSL 8% Wasting syndrome</td>
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<td></td>
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</tbody>
</table>

a χ² test.
b Paired t test of means, done using log-transformed values for CD4+ T cell count and HIV-1 viral load.
c P. carinii pneumonia; KS, Kaposi’s sarcoma; PCNSL, primary central nervous system lymphoma; N/A, not applicable.

d P. carinii pneumonia.
e Employed the FlipSCREEN Total IgE ELISA from ALerCHECK, Inc. Portland, ME.

![Image](https://via.placeholder.com/150)
wasting syndrome (n = 8) were the four most common initial AIDS diagnoses.

**Serum sCD23.** Levels of serum sCD23 in cases were compared to those in controls at each of the three CD4+ thresholds studied (Fig. 2). The natural log transformation of serum sCD23 was used to normalize the data for the t tests and regression models. The median serum sCD23 level in cases exceeded the median serum sCD23 level in controls at all three time points and three CD4+ thresholds; this difference was statistically significant at each time point and CD4+ threshold with the exception of the CD4+ threshold 0–99 (Table 2). Serum sCD23 was unrelated to AIDS-defining diagnosis in controls, and in a multivariate linear regression model AIDS-defining diagnosis was not significantly associated with serum sCD23 after, adjusting for case status (data not shown).

Serum sCD23 level was consistently the only correlate of AIDS NHL case status. Over 20 different covariates were entered in conditional logistic regression models because they had been previously reported as risk factors for either AIDS NHL or elevated serum sCD23. None of these were found to be significant predictors of case status (using a significance level of 0.05).

Serum sCD23 level was mildly associated with CD4+ T cell count in both cases and controls (Fig. 2, right panel). There were small but statistically significant positive correlations between serum sCD23 level and CD4+ T lymphocyte count, total T lymphocyte count, non-T lymphocyte count, and total lymphocyte count (Table 3). The correlations were slightly stronger for controls than for cases and strongest for non-T lymphocytes in cases.

As shown in Fig. 2, left panel, the difference in serum

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**Table 2** Median serum sCD23 (μg/liter) in AIDS NHL cases compared to median serum sCD23 in matched AIDS controls (μg/liter) in the MACS by both time and CD4+ threshold prior to each case’s AIDS NHL diagnosis

<table>
<thead>
<tr>
<th>Time prior to case’s NHL diagnosis (months)</th>
<th>CD4+ thresholds (cells/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6</td>
<td>6–12</td>
</tr>
<tr>
<td>n (pairs)</td>
<td>28</td>
</tr>
<tr>
<td>Case</td>
<td>6.41</td>
</tr>
<tr>
<td>Control</td>
<td>3.37</td>
</tr>
<tr>
<td>Pa *</td>
<td>0.0017</td>
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</tbody>
</table>

*Paired t test of log-transformed values.*
sCD23 level between cases and controls became more pronounced as time approached each case’s lymphoma diagnosis date. Interestingly, the difference was not due to increasing sCD23 in the cases but rather was due to decreasing serum sCD23 in the controls.

**Serum IgE**. Levels of serum IgE in cases were compared to those in controls at each of the time points and CD4+ thresholds studied. The natural log transformation of serum IgE was used to normalize the data for the t-tests and regression models. The median serum IgE level in cases exceeded the median levels in controls at all three CD4+ thresholds (0–99, 100–199, and 200–299) but at none of the three time points. However, a paired t test performed at each CD4+ threshold showed that the differences were not statistically significant (Table 4). Logistic regression confirmed that serum IgE did not predict of AIDS NHL. sCD23 and IgE were not correlated at any time point or CD4+ threshold (data not shown).

**Discussion**

Results of this study are consistent with previous work (12) in that serum sCD23 was elevated in HIV-positive patients who later developed AIDS NHL compared to those who developed AIDS without NHL. The magnitude of the difference seen by Yawetz et al. (12) was greater than that reported here, but the current findings, using a different sCD23 assay in a larger sample, lend support to the conclusion that serum sCD23 levels correlate with subsequent development of AIDS NHL. However, the small difference in median serum sCD23 levels between cases and controls indicates that serum sCD23 may not be an informative diagnostic test for preclinical AIDS NHL.

This study is the first to document longitudinal patterns of serum sCD23 in AIDS NHL cases prior to NHL diagnosis compared to controls. The more pronounced difference as time approached the lymphoma diagnosis date was not an unexpected pattern (Fig. 2, left panel). However, the expected cause of the increasing difference was controls’ sCD23 level remaining fairly constant over time, whereas the cases’ sCD23 level increased. Instead, the cases’ sCD23 level remained fairly constant, whereas the controls’ sCD23 level dropped dramatically. In contrast, serum sCD23 in B-CLL cases increases over time in proportion to tumor burden (19). It is this significant increase over time that makes serum sCD23 a useful disease marker for B-CLL; there is a threshold value above which a disease state is likely to occur. The stable levels of serum sCD23 over time in cases is additional evidence that serum sCD23 may not make a useful tool for diagnosis or management of AIDS NHL patients.

Results from this study indicate that serum sCD23 may decline as HIV infection progresses and the number of circulating lymphocytes decreases. Both cases’ and controls’ sCD23 levels varied as a function of CD4+ threshold (Fig. 2, right panel), and there were small but statistically significant positive correlations between sCD23 and lymphocyte counts in both cases and controls (Table 3). This is a new finding, as Yawetz et al. (12) reported no correlation between sCD23 and CD4+ T cells in their cross-sectional study. The association of serum sCD23 with lymphocyte counts is plausible, as interactions between B and T lymphocytes induce CD23 expression on B cells. However, cases did not experience the same HIV-mediated sCD23 decline as controls. Thus, the immunological processes leading to lymphomagenesis may stabilize sCD23 levels in AIDS NHL cases by increasing the amount of sCD23 produced by an immune system that would, in the absence of NHL, produce less sCD23 as the number and activity of immune cells decreased. Indeed, the correlations between sCD23 and lymphocyte counts were stronger for controls than for cases (Table 3).

Serum sCD23 level may not be an informative marker for preclinical AIDS NHL, but its persistent elevation in AIDS NHL cases may help us understand the pathogenesis of this malignancy. In vitro studies have shown that sCD23 functions as a B cell growth factor, so sustained levels of serum sCD23 may reveal a step in the chain of events resulting in lymphomagenesis. Yawetz et al. (12) suggested that the chronic antigenic stimulation that takes place during HIV infection results in both increased immunoglobulin isotype switching and higher serum sCD23; the genetic errors that are more likely to occur during increased isotype switching (e.g., c-myc translocations) may lead to lymphomagenesis. Subsequently, Breen et al. (20) found elevated sCD23 to be associated with AIDS NHL patients having SNCLL, a histological subtype associated with c-myc translocations. An alternative theory is that sCD23 is elevated in patients having EBV-positive NHL. EBV has the ability to transform B cells to malignancy (21) and is found in approximately one-half of AIDS NHLs (10); it has also been shown to increase the amount of CD23 on the cell surface of B lymphocytes (22). However, we have observed AIDS NHL patients with EBV in their tumors to have lower serum sCD23 levels than AIDS NHL patients whose tumors were EBV-negative (23). As patients live longer with HIV, we may expect to see greater numbers of AIDS NHL cases, making pathogenetic research in this area important.

**Acknowledgments**

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**Table 4** Median serum IgE (IU/ml) in AIDS NHL cases compared to median serum IgE (IU/ml) in matched AIDS controls in the MACS by both time and CD4+ threshold prior to the case’s AIDS NHL diagnosis

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<td>25</td>
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<td>19</td>
<td>38</td>
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<tr>
<td>Control</td>
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<td>0.62</td>
<td>0.76</td>
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*Paired t test of log-transformed values.*

References

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