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Mosaic chromosomal alterations detected in men living with HIV and the relationship to non-Hodgkin lymphoma

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Abstract

Objectives: People living with HIV (PLWH) have elevated risk of non-Hodgkin lymphoma (NHL) and other diseases. Studying clonal hematopoiesis (CH), the clonal expansion of mutated hematopoietic stem cells, could provide insights regarding elevated NHL risk.

Design: Cohort analysis of participants in the Multicenter AIDS Cohort Study (N=5,979).

Methods: Mosaic chromosomal alterations (mCAs), a type of CH, were detected from genotyping array data using MoChA. We compared CH prevalence in men living with HIV (MLWH) to HIV-uninfected men using logistic regression, and among MLWH, assessed the associations of CH with NHL incidence and overall mortality using Poisson regression.

Results: Comparing MLWH to HIV-uninfected men, we observed no difference in the frequency of autosomal mCAs (3.9% vs. 3.6%, p-value=0.09) or mosaic loss of the Y chromosome (mLOY) (1.4% vs. 2.9%, p-value=0.13). Autosomal mCAs involving copy-neutral loss of heterozygosity (CN-LOH) of chromosome 14q were more common in MLWH. Among MLWH, mCAs were not associated with subsequent NHL incidence (autosomal mCA p-value=0.65, mLOY p-value=0.48). However, two MLWH with diffuse large B-cell lymphoma had overlapping CN-LOH mCAs on

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chromosome 19 spanning *U2AF2* (involved in RNA splicing), and one MLWH with Burkitt lymphoma had high-frequency mCAs involving chromosome 1 gain and chromosome 17 CN-LOH (cell fractions 22.1% and 25.0%, respectively). mCAs were not associated with mortality among MLWH (autosomal mCA p-value=0.52, mLOY p-value=0.93).

Conclusions: We found limited evidence for a relationship between HIV infection and mCAs. Although mCAs were not significantly associated with NHL, mCAs detected in several NHL cases indicate a need for further investigation.

Keywords

clonal hematopoiesis; non-Hodgkin lymphoma; human immunodeficiency virus; genetic mosaicism; chromosomal alteration

Introduction

Despite improvements with effective antiretroviral therapy, HIV infection is associated with elevated risk of non-Hodgkin lymphoma (NHL) [1]. The two most common AIDS-associated NHLs (diffuse large B-cell lymphoma [DLBCL] and Burkitt lymphoma) manifest common genomic changes, including large segments of chromosomal loss or gain [2]. HIV infection is also associated with increased risk for infections, cardiovascular disease, and other conditions associated with chronic inflammation and aging [3,4].

Clonal hematopoiesis (CH) is the presence of a detectable clonal sub-fraction of circulating leukocytes that differs genetically from the inherited germline. CH expansion can be driven by small mutations of a few base pairs, referred to as clonal hematopoiesis of indeterminate potential (CHIP) [5,6], or can involve large structural mosaic chromosomal alterations (mCAs) such as gains, losses, or copy-neutral loss of heterozygosity (CN-LOH) [7,8]. CH increases in frequency with age and is associated with increased risk of infection and hematologic malignancies [5–9]. CHIP occurs more frequently among people living with HIV (PLWH) compared to HIV-free controls [10–14], and clone size is larger among PLWH [12]. However, studies of mCAs in PLWH have not been performed.

With improved survival, PLWH are aging, which translates into rising age-related comorbidity [15], promoting a need for markers that identify PLWH at elevated risk for NHL and other HIV-associated outcomes. Our study aimed to identify potential relationships between HIV infection, mCAs, NHL, and mortality in a population of 5,979 men living with HIV (MLWH) and men without HIV infection.

Methods

Study population

Starting in 1984, the Multicenter AIDS Cohort Study (MACS) enrolled men who have sex with men with HIV or at risk of acquiring HIV [16,17]. Participants were evaluated twice yearly for health assessment, blood collection, and HIV testing. NHL diagnoses were confirmed by medical records and cancer registry data. All participants provided informed consent.

Genotyping and mosaicism detection

Peripheral blood DNA was genotyped using the Illumina Multi-Ethnic Genotyping Array at the MACS visit with the greatest amount of available DNA. Raw genotyping array intensity data were used to calculate B allele frequencies and $\log_2$ R ratios which were utilized by MoChA (v2020–08-14) to detect mCAs [7] (Supplemental Methods, Supplementary Digital Content). Mosaic loss of chromosome Y (mLOY) detection utilized probes in the pseudoautosomal region [18]. Included samples had a genotyping call rate ≥96%, and mCAs were restricted to >2 megabases (Mb) to minimize false positives.

Statistical Analyses

HIV status refers to when the genotyped blood sample was collected (baseline). A total of 6,170 samples were scanned for mCAs. We removed duplicate observations (n=1) and samples with unknown collection date/no follow-up time (n=165) or conflicting data on HIV status at sample collection (n=13), resulting in 5,979 included participants.

Logistic regression examined associations of autosomal mCA and mLOY with HIV, adjusting for established mCA risk factors: age per decade, age^2 per decade^2, and smoking status (never, former, current). For analyses where mCA was not the outcome of interest, we categorized age into groups (<35, 35–44, 45–54, and 55+ years). Fisher exact tests were used to identify differences in mCA distribution.

Poisson regression examined the relationship between mCAs and NHL incidence among MLWH, with follow-up starting at the baseline timepoint. The analysis was unadjusted due to the limited number of NHL events. Poisson regression was also used to assess the association between mCAs and mortality among MLWH, adjusting for age group, calendar year at entry, and smoking status. All statistical tests were two-sided (α=0.05).

Results

Fifty-three percent of the 5,979 included MACS participants had HIV infection at baseline (Table S1, Supplemental Digital Content). Most participants were non-Hispanic White (74%), and MLWH were significantly younger than HIV-uninfected participants. Approximately one-third (36%) of MLWH were currently smoking.

We identified 223 individuals (3.7%) with at least one detectable autosomal mCA and 127 (2.1%) with mLOY (Table S2, Supplemental Digital Content). Autosomal mCA frequency was similar in MLWH and HIV-uninfected participants (3.9% vs. 3.6%), and, although mLOY appeared less common in MLWH (1.4% vs. 2.9%), multivariable analysis indicated HIV status was not significantly associated with the presence of autosomal mCAs (odds ratio [OR]=1.28, 95%CI=0.96–1.71, p-value=0.09) or mLOY (OR=0.73, 95%CI=0.49–1.09, p-value=0.13) (Table 1).

In analyses restricted to MLWH and adjusted for age and smoking status (Table S3, Supplemental Digital Content), no HIV-specific risk factors were associated with autosomal mCAs. Relative to MLWH with CD4 counts above 500 cells/mm^3, MLWH with CD4 counts below 350 cells/mm^3 had elevated mLOY frequency (OR=2.63, 95%CI=1.25–5.48,

p-value=9.8×10^{-3}). Antiretroviral therapy and baseline HIV viral load were not associated with mCAs (Table S3, Supplemental Digital Content).

We observed differences in the distribution of mCAs comparing MLWH to HIV-uninfected men. Chromosome 14 CN-LOH mCAs were more common in MLWH (N=12 events vs. N=1 in HIV-uninfected men, p-value=0.003) (Figure 1; Table S4, Supplemental Digital Content), frequently impacting the q arm spanning chr14:102,902,329–107,349,540 (GRCh37) (Figures S1 and S2, Supplemental Digital Content). In addition, chromosome 1 gains and chromosome 11 losses were present only among HIV-uninfected men (p-values 0.028 and 0.028, respectively, based on N=5 and N=5 events) (Table S4, Supplemental Digital Content).

NHL was diagnosed in 203 participants (16 prevalent cases and 187 incident cases), most of whom were MLWH (N=187, 92.1%). Incident NHL was diagnosed in 177 MLWH (5.7%), with DLBCL being the most common subtype (N=64) followed by central nervous system lymphoma (N=51), Burkitt lymphoma (N=18), and other/unspecified lymphoma (N=54).

Nine autosomal mCAs (7 copy-neutral events, 2 gains) and 4 mLOY events were detected in 11 participants with prevalent or incident NHL (Table S5, Supplemental Digital Content). Among MLWH with incident NHL, 8 had an mCA at baseline (5 autosomal mCA, 3 mLOY, Table S5, Supplemental Digital Content). The presence of mCAs was not significantly associated with NHL incidence among MLWH (p=0.65 for autosomal mCAs, p=0.48 for mLOY; Table S6, Supplemental Digital Content). However, the time from baseline until NHL diagnosis was shorter for MLWH with detectable mCAs (median 0.46 years, interquartile range [IQR] 0.22–0.60, range=0.02–1.02) than for those with no detectable mCA (median 3.76 years, IQR=1.28–6.15 years, range=0.06–21; p-value=7×10^{-5}).

Two MLWH with incident DLBCL (participants 2 and 6) had CN-LOH mCAs that involved an overlapping region on chromosome 19 that included *U2AF2* (Table S5, Supplemental Digital Content), a gene involved in RNA splicing [19]. The highest mCA cell fractions were observed in participant 1, a 25-year-old MLWH with Burkitt lymphoma diagnosed 8 days after sample collection who had a chromosome 1 gain (22.1% of cells) and chromosome 17 CN-LOH event (25.0%) that spanned *SETDB1* and *SRSF2*, respectively. *SETDB1* encodes a histone methyltransferase involved in transcriptional repression, and *SRSF2* encodes a pre-mRNA splicing factor involved in protein translation [20,21].

A total of 1,732 deaths were observed in MLWH, among whom 67 (2.1%) had autosomal mCAs and 16 (0.5%) had mLOY at baseline. In multivariable models adjusted for age, calendar year, and smoking status (Table S7, Supplemental Digital Content), mortality was not associated with presence of autosomal mCAs (mortality rate ratio 1.16, 95%CI 0.90–1.47, p-value=0.23) or mLOY (1.19, 0.69–1.91, p-value=0.49).

Discussion

In this large study of MLWH and HIV-uninfected men, the similarity in the frequency of mCAs by HIV status suggests that HIV infection does not notably impact overall clonal expansion of leukocytes with autosomal mCAs and mLOY. Chromosome 14 CN-LOH

events were more common among MLWH, although we could not identify any genes plausibly related to HIV, CH, or myeloid or lymphoid malignancies in the minimally impacted region [10,22]. In addition, while no overall association between HIV infection and mLOY was observed, MLWH with the lowest CD4 cell counts (<350 cells/mm^2) had a higher frequency of mLOY compared to those with CD4 cell counts of 500+ cells/mm^2. Future studies may identify important genes in these regions relevant to clonal expansion in the presence of HIV.

Previous work identified an association between HIV and an increased frequency of CHIP, in which single base pair alterations occur primarily in myeloid driver genes [10–13]. However, CHIP and mCAs differentially impact protein products and gene expression, potentially explaining observed differences of association. Likewise, the null association of mCAs with mortality among MLWH is contrary to previous reports from larger CH studies in the general population [23]. Future studies that investigate both types of CH jointly will be beneficial in understanding how CH is related to HIV and HIV-associated outcomes.

We did not observe an association between mCAs and subsequent NHL incidence among MLWH. In interpreting this null association, one possible explanation is that mCAs are not etiologically relevant. However, an alternative interpretation is that the time interval between the baseline blood sample and NHL diagnosis was too long for most NHL cases. Of note, the time between sample collection and NHL diagnosis was a year or less among the incident NHL cases who had an autosomal mCA or mLOY, suggesting that mCAs arise late in the development of NHL and that the sampling timeframe could be a critical component for detecting emerging neoplastic clones.

If mCAs arise late in the course of NHL development, expanded cell clones would likely include mutations in the same genomic regions found in NHL tumors; however, incident NHL cases among MLWH had no genomic regions that were generally elevated in mCA frequency. None of the mCAs among MLWH diagnosed with DLBCL encompassed genes previously identified as chromosomal translocation targets in HIV-related DLBCL (e.g., *BLC2*, *BLC6*, and *MYC*) [2]. Among the 8 DLBCL cases with autosomal mCAs, two had mCAs in a region that includes the chromosome 19 gene *U2AF2. U2AF2* mutations have been associated with hematological malignancies, but not specifically NHL [24–27]. In addition, the highest mCA cell fraction was observed in a man who developed Burkitt lymphoma within days of baseline. His mCAs encompassed *SETDB1* and *SRSF2,* both of which are mutated in other hematologic malignancies [28–30].

The present study is the first to examine the relationships of mCAs with NHL and mortality among MLWH. We used prospectively collected blood samples and employed robust methods that detected mCAs in the MACS study down to cell fractions of 0.6% and 2.6% for autosomal and mLOY events, respectively. As analyses were restricted to men, the findings may not be generalizable to women living with HIV. In addition, the low frequency of mCAs could be due to the age of the MACS study population and the timing of blood sample collection relative to NHL diagnosis.

In conclusion, we found limited evidence for a relationship between HIV infection and mCAs, although the enrichment among MLWH of copy-neutral mCAs on chromosome 14, mCAs encompassing *U2AF2* in two DLBCL cases, and mCAs spanning *SETDB1* and *SRSF2* in one Burkitt lymphoma case may warrant further investigation. Future studies examining the relationship between mCAs and NHL risk should examine blood samples collected closer in time to NHL diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Shu-Hong Lin – performed statistical analyses, drafted the manuscript

Sairah M. Khan – performed statistical analyses, drafted the manuscript

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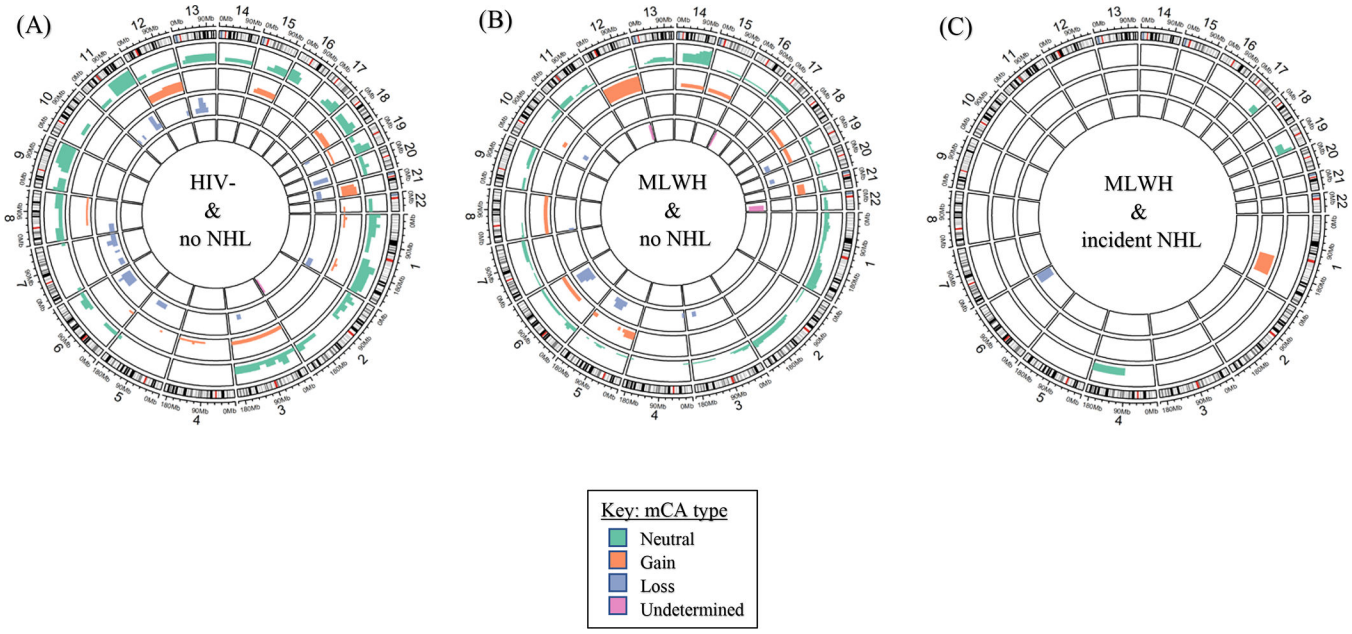

Figure 1.

Circos plots displaying the frequency and type of autosomal mosaic chromosomal alteration (mCA) by HIV and non-Hodgkin lymphoma (NHL) status. Participants with NHL diagnosed before the blood draw are not included in these analyses. (A) HIV-uninfected participants with no record of incident or prevalent NHL, (B) Men living with HIV (MLWH) with no record of incident or prevalent NHL, and (C) MLWH with incident NHL. The height of the colored bars indicates the number of participants with mCA in the specified chromosomal region

Table 1.

Multivariable associations of mosaic chromosomal alterations with HIV infection, smoking, and age

		Autosomal mCA				mLOY			
Exposure	**Subjects**	**N**	**%**	**Adjusted OR (95% CI)**	**P Value***	**N**	**%**	**Adjusted OR (95% CI)**	**P-Value***
HIV status					0.09				0.13
Without	2840	102	3.6%	reference		83	2.9%	reference	
Living With	3139	121	3.9%	1.28 (0.96, 1.71)		44	1.4%	0.73 (0.49, 1.09)	
Age, per decade	5979	223	3.7%	0.95 (0.49, 1.91)	0.88	127	2.1%	2.06 (0.64, 7.39)	0.23
Age^2, per decade^2	5979	223	3.7%	1.05 (0.99, 1.12)	0.13	127	2.1%	1.04 (0.93, 1.15)	0.46
Smoking status					0.54				0.29
Never	1817	63	3.5%	reference		33	1.8%	reference	
Former	1988	83	4.2%	1.01 (0.72, 1.42)		65	3.3%	1.30 (0.83, 2.05)	
Current	1863	64	3.4%	1.20 (0.84, 1.73)		25	1.3%	1.54 (0.87, 2.69)	

* Likelihood ratio test p-value

Abbreviations: CI confidence interval; mCA mosaic chromosomal alterations; OR odds ratio