High Prevalence of Clonal Hematopoiesis among Older People with HIV and Kaposi sarcoma

Poster 793

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BACKGROUND

- Clonal hematopoiesis (CH) is the presence of somatically mutated hemopoietic progenitor cells without overt signs of hematologic abnormalities.
- CH is an age-related phenomenon that is associated with increased mortality.
- High prevalence of CH has been separately described in cohorts of people with HIV (PWH) with varying CD4+ T cell counts and in patients with cancer.
- In a recent cross-sectional analysis of PWH and solid organ cancer types, CH prevalence was 23%.
- Kaposi sarcoma (KS) is an HIV-associated malignancy caused by Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus-8 (HHV8)
- Classic KS is known to impact older people without HIV and as people age with HIV, we expect high prevalence of CH among older people with HIV and KS.

We investigated clonal hematopoiesis (CH) prevalence and methylation assessment among older people with HIV and Kaposi sarcoma

METHODS

- In this retrospective analysis samples from participants with KS over 50 years of age, with and without other KSHV-associated diseases (KAD, such as multicentric Castleman disease (MCD) or KSHV-associated inflammatory cytokine syndrome) were investigated. (**Figure 1**).
- Stored samples pre- and post treatment were obtained from participants in HIV and AIDS Malignancy Branch at the NCI who consented to Protocol NCT03300830, and samples were sent to Moffit Cancer Center for analysis.
- Peripheral blood DNA was extracted from patient samples and used for CH detection and epigenetic methylation assessment. CH detection was performed using a custom Agilent SureSelectXTHS2 library preparation and target enrichment kit, which captured whole exons of 76 genes commonly mutated in CH and hematologic malignancies.
- Germline variant filtering included consideration of variant allele frequency (VAF) and recurrent presence in reference non-cancer populations. The 850K MethylationEPIC v1 BeadChip was used to capture genome-wide methylation status. DNA methylation-based biological age acceleration was calculated using epigenetic clocks, including Hovarth, PhenoAge, Frailty, GrimAge, and DunedinPACE (estimates pace of aging).

Statistical analysis - Baseline characteristics were evaluated prior to treatment. Fisher's exact tests were used to compare mutation status by clinical characteristics. Kaplan-Meier method and Cox proportional hazard ratio was used to evaluate survival among participants with and without CH mutations at baseline.

In a small study of 17 people with HIV and Kaposi sarcoma over 50 years of age, clonal hematopoiesis was detected in **59%** of patients

There was an association between low CD4 T cell counts and accelerated aging in this population.

RESULTS

- Samples from 17 male PWH with a median age of 55 years were included in these analyses (**Table 1**).
- The median duration of KS was 2.7 years and HIV infection was 15 years.
- At the time of these analyses, the median HIV viral load was <20 copies/mL and median CD4⁺ T cell count was 126 cells/µL.
- The majority of patients had a diagnosis of KS alone and 53% had received prior treatment for KS.
- The median KSHV viral load in the PBMCs was 270 copies/10^6 cells.
- All participants had a baseline sample, and 14 participants had a post-treatment sample evaluated.
- Treatment regimens that were administered included liposomal doxorubicin alone for KS or in combination with pomalidomide or rituximab for KS and other KAD

Table 1: Baseline Characteristics

Age, years, median (IQR)	55 (54, 58)
Sex, n (%)	
Male	17 (100)
Race, n (%)	
Black	6 (35)
White	9 (53)
Other	2 (12)
Time from KS diagnosis, years, median (IQR)	2.7 (0.2, 8.9)
Time from HIV diagnosis, years, median (IQR)	15.0 (6.0, 20.8)
Median CD4 count, cells/µL, (IQR)	126 (83, 329)
Median HIV VL, copies/mL, (IQR)	<20 (20, 262)
Prior KS chemotherapy (%)	9 (53)
KSHV disease characteristics, n (%)	
KS alone	10 (59)
KS with MCD	3 (17)
KS with KICS	4 (24)
KSHV viral load, PBMCs, copies/10^6 cells, median (IQR)	270 (0, 2863)

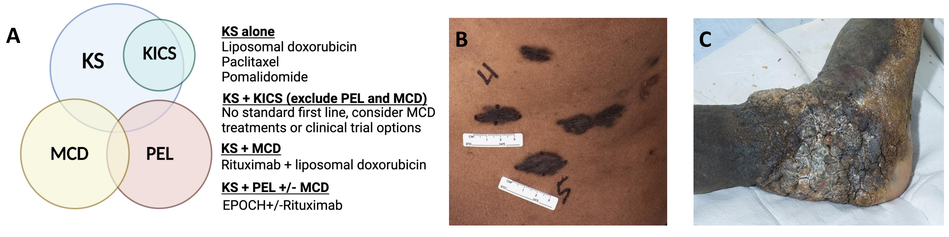


Figure 1 – A. The overlap of KS with other KSHV-associated diseases and types of treatments administered **B and C.** KS manifestations of the skin in older people with HIV.

RESULTS

- CH was detected in 10 of 17 participants (59%) at baseline before KAD-directed therapy; 6 participants (35%) harbored CH mutations with >2% VAF. These genes included TP53, DNMT3A, ASXL1, BCORL1.
- On evaluation of methylation patterns indicative of advanced biologic age, there was evidence of accelerated aging and risk of mortality when stratifying CD4 T cell count using two biologic clocks (**Figure 2**).
- Among participants with KS with CD4 T cell counts <200 cells/µl, CH mutation prevalence was 41% compared to 18% for those with counts ≥200 cells/µl. However, this difference was not statistically significant (P=0.3).
- By the end of 5 years, 1 of the 10 participants with a CH mutation at baseline remained alive (CHIP=1, 10% survival) compared to 3 of the 7 participants without a CH mutation (CHIP=0, 43% survival). This difference was not statistically significant (P=0.36, **Figure 3**)

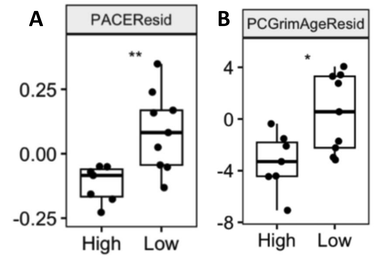


Figure 2 – Aging clocks stratified by CD4 T cell count high (≥200 cells/µL) and low (<200 cells/µl) A. DunedinPACE clock highlighting accelerated aging B. GrimAge clock reflects risk of mortality

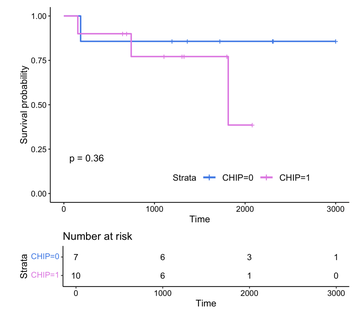


Figure 3 – Survival of KS among participants by presence of CH mutation

- All 7 participants who had CH present at baseline and received KS-directed therapy had persistent CH detectable after treatment.
- There was no changes in epigenetic clock measurements between the two timepoints.

CONCLUSIONS

As compared to existing data on CH mutations in PWH or in populations with cancer, there is a high prevalence of CH mutations in this small study of older PWH and KS and other KAD.

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