Clinical Impact of Kaposi Sarcoma Herpesvirus Subtypes on Disease Outcomes

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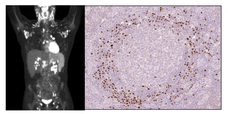
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BACKGROUND

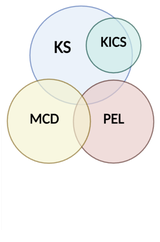
- Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus 8, is a large double-stranded DNA virus that causes several KSHV-associated diseases (KAD - **Figure 1**).
- Genetic analysis has primarily focused on variable regions, particularly the K1 and K15 open reading frames (ORFs).
- Major genetic subtypes based on K1—A, A5, B, C, D, E, and F—are identified in specific geographic areas with subtype A and C being most common in North America.
- A few studies have shown that certain KSHV subtypes may be linked to more aggressive disease, but larger cohort studies are necessary to confirm these findings.

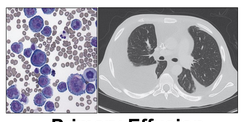


Kaposi sarcoma (KS)



Multicentric Castleman Disease (MCD)





Primary Effusion Lymphoma (PEL)

Figure 1. KSHV-associated Diseases (KAD) and their manifestations.
These conditions can occur alone or concurrently in the same patient. KSHV inflammatory cytokine syndrome (KICS) is a diagnosis of exclusion of MCD and PEL.

OBJECTIVES

To investigate the association between KSHV subtypes and clinical outcomes in patients with KSHV-associated diseases (KAD).

METHODS

- This retrospective study included 161 participants treated at the NIH by the HIV/AIDS Malignancy Branch (HAMB) between 2000 and 2025 with clinical information obtained at the time of treatment.
- KSHV testing was conducted on saliva, blood, pleural fluid, bronchoalveolar lavage or tissue.
- K1 gene sequences were obtained using a combination of next-generation whole-genome sequencing and targeted Sanger sequencing through nested PCR. (**Figure 2**)
- Survival analysis was evaluated using the Kaplan-Meier method and log-rank tests were used to compare outcomes by KAD and/or KSHV subtype.
- Wilcoxon rank sum test was used to evaluate characteristics among patients with PEL with and without subtype A.
- Cox proportional hazard model for overall survival was evaluated for key clinical characteristics at the time of treatment for KAD at NIH.

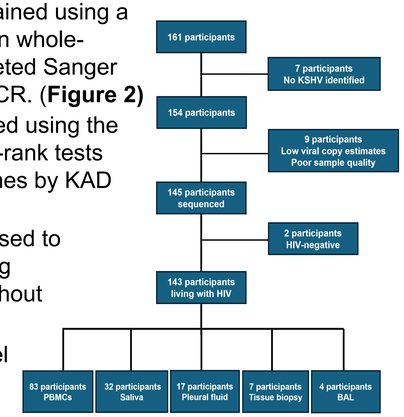


Figure 2. Consort diagram
Analyses of participants included in the cohort and the specimens used to characterize KSHV subtype

KSHV-associated disease (KAD) diagnoses rather than KSHV subtype influenced survival outcomes in patients with KAD.

RESULTS

- Among 143 patients included in the study, KSHV subtype A was most frequent subtype, followed by subtype C. KSHV subtypes did not differ by KAD diagnosis (**Table 1**).
- Survival differences were driven the by presence of concurrent KAD or a PEL diagnosis but not by the KSHV subtype (**Figure 3**)

	All	KS	KS+MCD	KS+KICS	PEL+/-MCD+/-KS
Participants n, (%)	143 (100)	57 (40)	17 (12)	24 (17)	45 (31)
Age, years, median (IQR)	39 (31, 51)	37 (29, 49)	41 (33, 52)	38 (32, 47)	40 (32, 54)
Gender					
Male n, (%)	135 (94)	55 (96)	16 (94)	22 (92)	42 (93)
Female n, (%)	8 (6)	2 (4)	1 (6)	2 (8)	3 (7)
Race/Ethnicity					
White n, (%)	43 (30)	18 (32)	6 (35)	2 (8)	17 (38)
Black n, (%)	75 (52)	27 (47)	7 (41)	20 (84)	21 (49)
Asian n, (%)	3 (2)	3 (5)	0	0	0
Hispanic n, (%)	22 (15)	9 (16)	4 (24)	2 (8)	7 (13)
KS Staging					
T0	18 (13)	8 (14)	3 (18)	0	7 (16)
T1	113 (79)	49 (86)	14 (82)	24 (100)	26 (58)
Visceral involvement	76 (54)	25 (44)	13 (76)	20 (83)	19 (42)
Deceased n, (%)	46 (32)	6 (10)	3 (17)	7 (29)	30 (67)
HIV and KSHV characteristics					
HIV positive n, (%)	143 (100)	57 (100)	17 (100)	24 (100)	45 (100)
CD4 T-cells, cells/µl, median (IQR)	170 (73, 379)	176 (79, 419)	116 (65, 202)	110 (64, 292)	173 (68, 400)
CD4 T-cells < 200 cells/µl, n (%)	81 (58)	31 (57)	12 (71)	13 (54)	25 (56)
HIV log copies/ml, median (IQR)	1.68 (1.3, 2.62)	1.8 (0, 2.82)	1.66 (1.3, 3.2)	1.64 (1.3, 2.1)	1.7 (1.3, 2.64)
HIV undetectable (<20 copies/ml), n(%)	49 (34)	18 (33)	7 (41)	9 (38)	15 (33)
KSHV copies/10^6cells, median, (IQR)	78445 (3203, 563823)	7182 (183, 131289)	187500 (118337, 683540)	49740 (12058, 659338)	192000 (26913, 10181158)
KSHV <100K copies/10^6 cells, n (%)	76 (54)	40 (74)	3 (18)	14 (58)	19 (42)
KSHV Subtypes					
Subtype A n, (%)	66 (46)	30 (52)	5 (29)	10 (42)	21 (47)
Subtype A5 n, (%)	4 (3)	1 (2)	0	0	3 (7)
Subtype B n, (%)	12 (8)	3 (5)	2 (12)	1 (4)	6 (13)
Subtype C n, (%)	39 (27)	16 (28)	5 (29)	8 (33)	10 (22)
Subtype E n, (%)	4 (3)	1 (2)	3 (18)	0	0
Subtype F n, (%)	2 (2)	0	0	2 (8)	0
Mixed Subtypes n, (%)	16 (11)	6 (11)	2 (12)	3 (13)	5 (11)

Table 1. Demographic and clinical characteristics of 143 patients with HIV and KSHV-associated diseases.

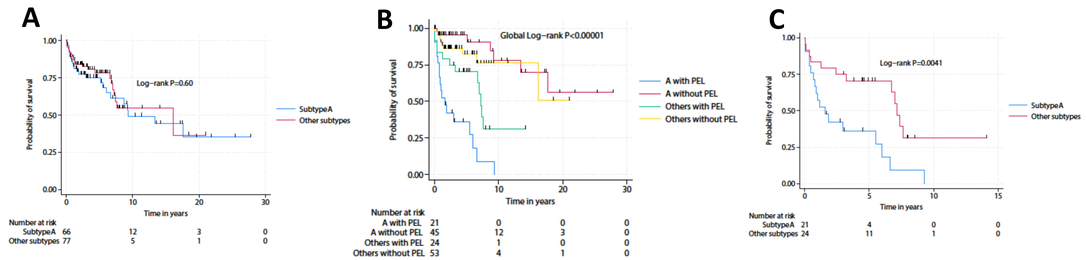


Figure 3. Kaplan-Meier curves demonstrating overall survival by KAD characteristics and KSHV subtypes.
(A)KSHV subtype A compared with other subtypes among patients who have KSHV-associated disease (B). Evaluation of Subtype A or other subtypes in patients diagnosed with or without PEL* (C).Comparison of Subtype A and other subtypes in patients with PEL *PEL diagnosis includes individuals diagnosed with PEL+/-MCD+/-KS.

	All patients with PEL	Subtype A and PEL	Other subtypes and PEL	P-value
Participants, n (%)	45 (100%)	21 (47)	24 (53)	
Age, years, median, (IQR)	40 (32, 54)	41 (31, 55)	39 (32, 51)	p=0.96
Hemoglobin g/dL	8.9 (7.4,10.6)	8.3 (7.4, 10.3)	9.8 (7.3, 12.3)	p=0.16
Platelets K/mcL	176 (53, 320)	176 (94, 340)	161 (37, 277)	p=0.56
Albumin g/dL	2.2 (1.9, 2.9)	2.1 (1.5, 2.3)	2.9 (2, 3.4)	p=0.009
LDH U/L	238 (163, 310)	199 (161, 265)	274 (176, 377)	p=0.34
CD4 T-cells cells/µl, median (IQR)	173 (68, 396)	250 (124, 421)	145 (43, 231)	p=0.10
KSHV copies/10^6cell/ml, median, (IQR)	192,000 (21735, 9130435)	100,000 (16975, 2323279)	522,728 (59434, 45763636)	p=0.18
ECOG				
0-2, n (%)	26 (58)	12 (57)	14 (58)	p=0.69
3-4, n (%)	19 (42)	9 (43)	10 (42)	
EBER positive, n (%)	26 (58)	11 (52)	15 (63)	p=0.46

Table 2. Analysis of patients with Primary Effusion Lymphoma.

RESULTS

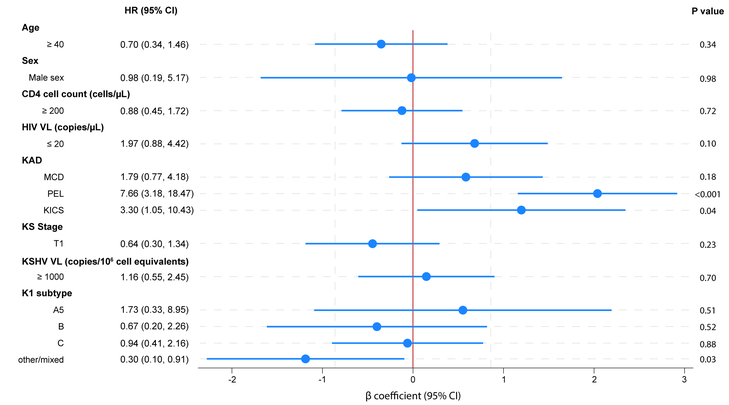


Figure 4. Forest plot of Cox Proportional Hazard Ratio for overall survival
Evaluating key clinical characteristics, KAD diagnosis and KSHV subtype the hazard ratio for each independent variable with the point estimate represented by the dot and the 95% confidence interval represented by the line.

- Baseline demographics (age, sex or CD4 T cell count) did not impact survival differences (**Figure 4**)
- Patients diagnosed with KICS+KS or PEL+/- other KADs had poor outcomes, whereas KS and MCD diagnoses were not associated with survival.
- Having other K1 genotypes (E, F) or a mixed infection (i.e. A and C) is associated with improved outcomes in comparison to subtype A infection, however, this may be due to limited numbers

Presence of KSHV subtype A may confer poor outcomes among patients diagnosed with PEL

- Among 45 patients with PEL with and without MCD and/or KS, individuals infected with Subtype A had significantly poorer survival compared to those with other subtypes (**Figure 3C**).
- Patients with PEL with Subtype A as compared to other KSHV subtypes, demonstrate a trend toward lower serum albumin levels, a recognized marker of malnutrition and inflammation (**Table 2**).

CONCLUSIONS

- KSHV subtypes did not vary by KAD diagnoses
- Survival outcomes were driven by the presence of concurrent KAD, specifically a diagnosis of PEL was associated with worse outcome rather than KSHV subtype.
- Among patients with PEL, presence of subtype A was associated with poor survival as compared to other KSHV subtypes.

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