Study of Characteristics and Outcomes of Kaposi sarcoma herpesvirus associated inflammatory cytokine syndrome (KICS)

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BACKGROUND

- Kaposi sarcoma herpesvirus (KSHV, also called human herpesvirus-8) causes Kaposi sarcoma (KS), a plasmablastic form of multicentric Castleman disease (MCD), a form of non-Hodgkin lymphoma known as primary effusion lymphoma (PEL) and more recently a KSHV inflammatory cytokine syndrome (KICS).
- KICS is characterized by severe inflammatory signs (elevated C-reactive protein, elevated KSHV viral load) and symptoms. The initial diagnostic criteria of KICS only excluded MCD.
- KICS, which occurs among people with HIV (PWH) and KS, has overlapping clinical features of PEL. It is important to appropriately diagnose KICS and PEL as the treatments for these conditions are different.

We present findings from the largest prospective study of KICS

METHODS

The primary objective was to evaluate KICS natural history. There were broad eligibility criteria to allow diagnostic evaluation for KICS and exclusion of other KSHV-associated diseases and inflammatory disorders (**Figure 1**).

Baseline characteristics of those with KICS were compared with those who were diagnosed with PEL during the course of the study.

Participants (pts) with confirmed KICS were assigned to either an observation arm to treat KS with standard therapy or to a KICS treatment arm to receive rituximab-based regimens, high-dose zidovudine and valganciclovir (AZT/VGC) or other rational therapies, such as tocilizumab. Pts with PEL were treated with curative intent with multiagent chemotherapy.

Statistical analysis - Baseline characteristics were compared using Fisher's exact test, Chi square test and Wilcoxon Rank Sum test, as appropriate. Kaplan-Meier method was used to evaluate survival among participants with KICS and compared to those excluded for PEL within the study.

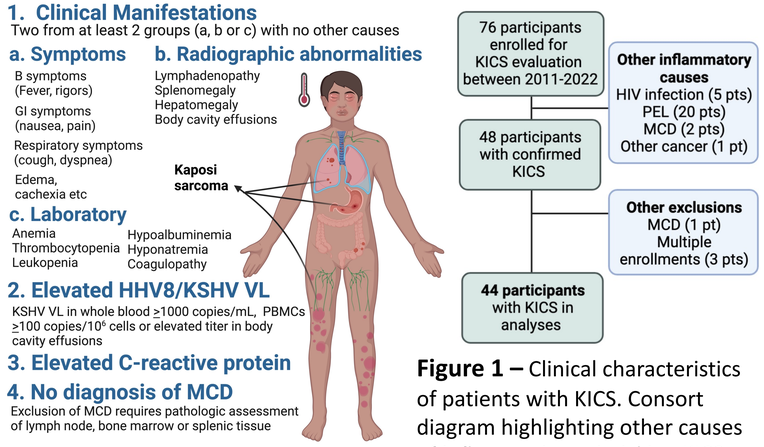


Figure 1 – Clinical characteristics of patients with KICS. Consort diagram highlighting other causes of inflammation mimicking KICS.

KICS may occur in patients with HIV and KS. It is a distinct diagnosis that requires the exclusion of other KSHV-associated diseases such as PEL and MCD

RESULTS

- Among 44 pts with confirmed KICS, all but one patient had a diagnosis of HIV. Thirty-eight pts with HIV (88%) were on antiretroviral therapy at baseline of KICS diagnosis.
- The median duration of HIV infection of those with KICS was 8.2 years median with an HIV viral load was 76 copies/mL and median CD4⁺ T cell count was 89 cells/µL (**Table 1**).
- Comparing baseline characteristics at study entry of pts with KICS and pts diagnosed with PEL, both clinical and HIV characteristics were similar. However, those diagnosed with PEL had lower albumin and higher ferritin as compared to those with KICS.
- Among all pts with confirmed KICS, 27 pts (61%) received KS-focused therapy alone, 18 pts (41%) received rituximab-based therapy [with liposomal doxorubicin (15) or paclitaxel (2) or without chemotherapy (1)], 1 pt received AZT/VGC, 1 pt received tocilizumab.
- Ten of 18 pts (55%) who received rituximab-based therapies had clinical benefit with improvement of KICS signs and symptoms within 8 weeks of treatment.

Table 1: Baseline Characteristics	KICS N=44	PEL N=20	P
Cisgender Male (%)	39 (89)	19 (95)	0.89
Age, years, median (IQR)	41 (32, 48)	45 (33, 56)	
HIV positive (%)	43 (98)	20 (100)	1.00
Time from HIV diagnosis, years, median (IQR)	8.2 (1.6, 15.2)	6.4 (1, 9.8)	0.58
Median CD4 count, cells/µL, (IQR)	89 (32, 155)	90 (28.5, 229)	0.77
Median HIV VL, copies/mL, (IQR)	76 (24, 3700)	122 (38, 1160)	0.72
Prior KS chemotherapy (%)	24 (55)	10 (50)	0.74
Hemoglobin, g/dL median, (IQR)	9.4 (8.2, 10.2)	9.3 (7.9, 9.9)	0.47
Platelets, K/mcL median, (IQR)	232 (149, 316.5)	207 (106, 293.3)	0.28
Albumin, g/dL median, (IQR)	3.1 (2.4, 3.6)	2.6 (2.2, 3)	0.03
C-Reactive Protein, mg/L median (IQR)	28.3 (9.5, 67)	32.1 (16.3, 72.9)	0.40
Ferritin, mcg/L median (IQR)	400.5 (200.5, 761)	786.5 (573.3, 1732.8)	0.005

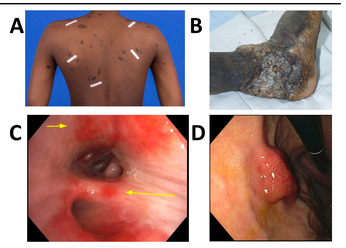


Figure 2 – Manifestations of concurrent KS of skin (A, B), lungs (C) and stomach (D) in patients presenting with KICS within the study.

RESULTS

- T1 KS was present in 43 of 44 pts with KICS (**Figure 2**) and following treatment for KS and KICS with study therapies, improvement in KS was noted in 16 pts.
- For pts with confirmed KICS, the median overall survival was 45.8 months (95% confidence interval: 20.3 – not reached).
- As compared with PEL, there was no difference in survival outcomes among those diagnosed with KICS. (**Figure 3**)

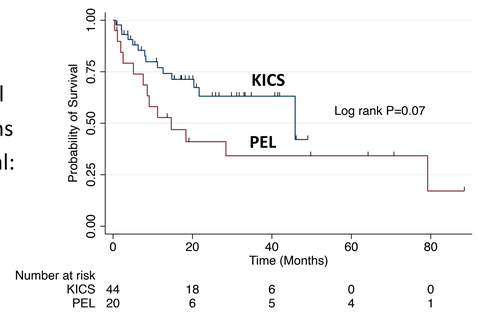
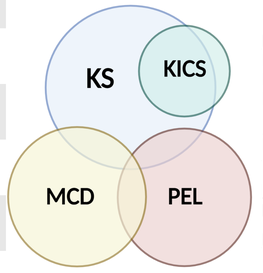


Figure 3 – Kaplan-Meier curve depicting the survival outcomes in patients with KICS as compared to PEL

CONCLUSIONS

Within the spectrum of KSHV-associated diseases, KICS is a distinct condition that often occurs with KS and carries a relatively poor survival (**Figure 4**). Pts should have extensive workup to rule out MCD and PEL prior to KICS diagnosis. Rituximab-based therapies may have a role in treatment of a subset of pts with KICS. Optimal therapy for individuals with KICS remains an active area of research.



KS alone
Liposomal doxorubicin
Paclitaxel
Pomalidomide

KS + KICS (exclude PEL and MCD)
No standard first line, consider MCD treatments or clinical trial options

KS + MCD
Rituximab + liposomal doxorubicin

KS + PEL +/- MCD
EPOCH+/-Rituximab

Figure 4 – The overlap of KSHV-associated diseases and treatments administered.

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