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BRIEF REPORT

Kaposi Sarcoma Herpesvirus Inflammatory Cytokine Syndrome–like Clinical Presentation in Human Immunodeficiency Virus–infected Children in Malawi

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We describe 7 human immunodeficiency virus–infected Malawian children with Kaposi sarcoma who met criteria for Kaposi sarcoma herpesvirus (KSHV) inflammatory cytokine syndrome. Each presented with persistent fevers, bulky lymphadenopathy, massive hepatosplenomegaly, and severe cytopenias. Plasma analyses were performed in 2 patients, both demonstrating extreme elevations of KSHV viral load and interleukin 6.

Keywords. Kaposi sarcoma; Kaposi sarcoma herpesvirus; human herpesvirus 8; Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; pediatric oncology.

Kaposi sarcoma (KS)–associated herpesvirus (KSHV) inflammatory cytokine syndrome (KICS) is a systemic illness that typically occurs in association with KS [1–3]. Unlike most KS, KICS shares mechanisms of viral pathophysiology with KSHV-associated multicentric Castleman disease (MCD)—uncontrolled lytic phase KSHV infection resulting in extremely high viral load (VL), viral interleukin 6 (IL-6), human IL-6, and IL-10 levels [1–4]. KSHV viremia is also associated with lymphadenopathic KS in children in Malawi [5, 6]. Neither pediatric MCD nor KICS has been reported in KSHV-endemic regions [7].

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METHODS

Patient Selection/Working Case Definition

Utilizing the adult KICS case definition [1–3], we identified 9 children from Lilongwe, Malawi, with human immunodeficiency virus (HIV)–related KS—6 from a retrospective cohort (n = 67) and 3 from a prospective study that included virologic analyses of KSHV (n = 24) [6, 8]. We revised a working case definition for pediatric KICS to only include a distinct recurring pattern of clinical features observed in 7 patients with all of the following: bulky lymphadenopathy (aggregate diameter >6 cm), severe pancytopenia (platelet count <50 000 cells/μL and hemoglobin <8 g/dL), persistent fevers (temperature >38°C, not associated with underlying infection), and massive, palpable hepatosplenomegaly extending toward the umbilicus. Two patients from the prospective study were excluded from the pediatric KICS definition; although they presented with bulky lymphadenopathy, severe thrombocytopenia, KSHV VL values of 6.4×10^3 and 1.7×10^4 copies/mL, elevated IL-6 (28.3 and 12.7 pg/mL), and absence of histologic features of MCD on lymph node biopsy, they lacked palpable hepatosplenomegaly or persistent fevers. Without virologic testing, they would have been clinically categorized as lymphadenopathic KS. Because availability of KSHV VL testing is rare in Africa, this case definition for pediatric KICS is clinically derived.

Diagnostic Confirmation

In light of severe thrombocytopenia without reliable access to platelet transfusion, diagnostic biopsies were not feasible initially. However, after observing rapid normalization of platelet counts after initiating therapy in the first 3 patients, the diagnostic approach thereafter included incisional lymph node biopsy in patients with resolution of thrombocytopenia within 1 week of treatment initiation. Histological confirmation of lymph node KS without evidence of MCD was documented in patient 4, as well as the 2 excluded patients. Patient 5 was clinically diagnosed based on prototypical hyperpigmented KS skin lesions in addition to the features of KICS. Patients 6 and 7 presented critically ill with multiorgan failure and diagnostic biopsies were not performed. However, plasma samples from these 2 patients, plus the 2 excluded patients, were sent to a collaborating laboratory in the United States for virology and cytokine assessments [6]. C-reactive protein testing was not available.

Statistical and Ethical Considerations

We compared the 7 patients with pediatric KICS to the combined pediatric KS cohorts, and because of clinical overlap (eg, lymphadenopathy and cytopenias), we also

compared them to the subset with lymphadenopathic KS [6, 8, 9]. Statistical analyses were performed using Stata version 13.1 software. *P* values were generated using a k-sample equality-of-medians test or Fisher exact test. Ethical approvals were provided by the National Health Sciences Research Committee in Malawi and the Baylor College of Medicine Institutional Review Board. Guardians provided informed consent for patients enrolled prospectively.

RESULTS

Clinical and Laboratory Characteristics

The median age of children with KICS was 3.5 years (range, 2.2–6.2 years; Table 1). The range for platelet count was 6000–24 000 cells/μL and for hemoglobin 4.0–6.2 g/dL. Viral/cytokine assessments demonstrated extreme elevations of KSHV VL, human IL-6, and IL-10 levels in patients 6 and 7 (Table 1). Epstein-Barr VL was also elevated at 1.0×10^6 and 9.5×10^5 copies/mL, respectively. Chemistries were available solely for patient 7 (sodium 129 mmol/L, albumin 2.3 g/dL).

Treatment Response

The first patient demonstrated persistent fevers, lymphadenopathy, splenomegaly, and severe cytopenias despite 2 doses of bleomycin and vincristine (BV). This was atypical for lymphadenopathic KS because severe cytopenias and lymphadenopathy generally improve within 1–2 weeks of initiating BV (without steroids) [8]. Moreover, hepatosplenomegaly and persistent fevers are rarely observed in pediatric KS [5]. Hence, a presumptive diagnosis of KICS vs MCD was made. Without access to the standard agents used to treat MCD/KICS in high-income countries (eg rituximab, ganciclovir, or liposomal doxorubicin), prednisone was added to treat the systemic inflammatory syndrome. The platelet count increased from 7000 to 789 000 cells/μL within 1 week and fevers resolved; lymphadenopathy and splenomegaly completely normalized within 2–3 weeks.

All subsequent patients presenting with the entire constellation of findings described in our working case definition of pediatric KICS were treated with BV plus prednisone (persistent fevers and hepatosplenomegaly distinguish them

Table 1. Comparison of the Clinical and Virologic Characteristics Between Pediatric Kaposi Sarcoma (KS)–associated Herpesvirus Inflammatory Cytokine Syndrome and Pediatric KS in Malawi

		Combined Published Pediatric KS Cohorts				Published Adult KICS Cohorts	
Variable	Pediatric KICS	All Patients With KS	*P* Value	Lymphadenopathic KS	*P* Value	Retrospective	Prospective
No. of subjects	7	84		39		6	10
Age, y	3.5 (2.3–5.0)	8.8 (5.0–12.4)	.01[a]	5.4 (3.0–9.0)	.41[a]	38 (29–52)	36 (22–60)
Female sex, No. (%)	3 (43)	41 (49)	1.00[b]	12 (31)	.67[b]	NR	0
Persistent fevers, No. (%)	7 (100)	0	< .001[b]	0	< .001[b]	6 (100)	2 (20)
Massive hepatosplenomegaly, No. (%)	7 (100)	0	< .001[b]	0	< .001[b]	Not specified	0
Receiving ART, No. (%)	3 (43)	43 (51)	.71[b]	17 (44)	1.00[b]	4 (67)	8 (80)
Time on ART, mo	0.5, 12, and 12	7 (3–36)	…	24 (2–36)	…	[c]	NR
IRIS presentation, No. (%)	1 (14)	21 (25)	1.00[b]	8 (21)	1.00[b]	NR	NR
CD4 count, cells/μL	414 (365–440)	368 (216–690)	1.00[a]	494 (323–806)	.34[a]	255 (28–492)	88 (7–1038)
HIV viral load, copies/mL[d]	Suppressed and 17 535	97 196 (1332–329 391)	…	92 289 (502–458 300)	…	4650 (<50–1.1 million)	72 (<50–74 375)
Hemoglobin, g/dL	4.8 (4.4–5.5)	9.5 (7.7–10.4)	.01[a]	9.5 (7.0–10.1)	.01[a]	8.7 (7.0–14.8)	9.0 (6.5–10.2)
Platelet count	14 (7–20)	221 (126–377)	.01[a]	204 (67–378)	.01[a]	158 (62–231)	138 (27–371)
KSHV viral load, copies/mL[e]	19 000 and 656 154	425 (0–1190)	…	751 (376–4068)	…	31 872 (0–248 485)	81 968 (0–3.99 million)
Human IL-6, pg/mL[e]	450.0 and 19.1	8.2 (6.8–12.7)	…	10.8 (6.8–15.8)	…	34.3 (2.1–205.7)	14.6 (3.6–330.3)
IL-10, pg/mL[e]	320.0 and 419.7	18.4 (9.3–34.9)	…	18.1 (16.8–23.0)	…	494.0	36.5 (4.6–2357.2)

Analyses compare pediatric KICS to all pediatric KS patients as well as the subset with lymphadenopathic KS. Adult KICS data from the United States are also listed for contextual comparison. For age, CD4 count, HIV viral load, hemoglobin, platelet count, KSHV viral load, human IL-6, and IL-10 values, figures given are median and either interquartile range (pediatric data) or range (adult data).

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IL, interleukin; IRIS, immune reconstitution inflammatory syndrome; KICS, Kaposi sarcoma herpesvirus–associated inflammatory cytokine syndrome; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma–associated herpesvirus; NR, not reported.

[a]Fisher exact *P* value estimated from the k-sample equality of medians test.

[b]*P* value estimated using Fisher exact test.

[c]Time on ART for the retrospective adult KICS cohort was not specified; however, it was mentioned that 1 patient developed KICS within a month of starting ART, while 2 patients presented within a year of ART initiation.

[d]HIV viral load assessments were not routinely available in Malawi throughout much of the study time period; therefore, limited data are available. Among KICS subjects, 2 had baseline HIV viral load assessments, while among all subjects with KS and the subgroup with lymphadenopathic KS there were 21 and 11 subjects, respectively, who had baseline HIV viral load data available.

[e]KSHV viral load and cytokine assays were performed on plasma extracted from whole blood in pediatric and adult prospective cohorts, and on peripheral blood mononuclear cells in adult retrospective cohort. Virologic data were available for 17 of 84 from the entire pediatric KS cohort, and 8 of 39 from the subset analysis focused on children with lymphadenopathic KS.

from lymphadenopathic KS). The prednisone rationale was based on the corticosteroid strategy used in hemophagocytic lymphohistiocytosis (HLH) protocols [10]. The dose was 2 mg/kg/day for 2 weeks, followed by consecutive 2-week blocks at 1 mg/kg/day, 0.5 mg/kg/day, and 0.25 mg/kg/day, and tapered off over 1 week.

Thrombocytopenia improved (without transfusion) to a median platelet count of 587 000 cells/μL (range, 148 000–789 000 cells/μL) within 2 weeks of starting prednisone plus BV in 5 patients. Two patients died in the first week of presentation, 1 with respiratory failure and 1 from multiorgan failure. Another death occurred at home from suspected sepsis 1 month after initiating therapy in a patient who had achieved clinical complete remission and normalization of cytopenias prior to discharge. Four patients achieved sustained complete remission (median follow-up, 44 months [range, 31–50 months]), continuing on ART.

KICS Versus KS Without KICS

Children with KICS were younger than the pediatric KS cohort ($P = .01$), were more likely to present with persistent fevers and hepatosplenomegaly ($P < .001$), and presented with more severe anemia and thrombocytopenia compared to pediatric KS patients overall ($P = .01$) and those with lymphadenopathic KS ($P = .01$). There was no difference in percentage of patients on ART, presentation in context of an immune reconstitution inflammatory syndrome (IRIS), or CD4 count (Table 1). One patient with KICS presented within 2 weeks of ART initiation, and distinction between KICS and KS IRIS was challenging due to limitations in reevaluating the trend in CD4 count and HIV VL. Two patients presented 12 months after ART initiation, thus not consistent with IRIS.

Pediatric Versus Adult KICS

Although small sample sizes of pediatric and adult KICS cohorts preclude definitive statistical comparison, we observed comparable extreme elevations in KSHV VL, IL-6, and IL-10 levels in the pediatric cohort. Additionally, hepatosplenomegaly and extreme cytopenias appear to be prominent in pediatric KICS.

DISCUSSION

This case series represents the first description of HIV-infected children with KICS. We define pediatric KICS in KSHV-endemic regions by a constellation of clinical findings including persistent fevers, bulky lymphadenopathy, severe thrombocytopenia/anemia, *and* massive hepatosplenomegaly. KICS in children represents a subset of pediatric KS accompanied by extreme inflammation and elevated KSHV VL. Its clinical features appear to be driven by inflammatory cytokines and long-term complete remission was achievable despite severe limitations on medical resources by adding prednisone to chemotherapy plus ART.

Prednisone has been associated with a worsening of adult KS; therefore, its use should be considered cautiously in children with KS [11, 12]. Our approach only calls for the addition of steroids to BV in those patients who fulfill all 4 clinical criteria in the working case definition of pediatric KICS listed above, and in the context of lacking other therapeutic options (eg, etoposide, rituximab, ganciclovir, or anti-IL-6 agents).

The 2 pediatric KICS patients with KSHV VL and IL-6/IL-10 assessments demonstrated extreme elevations consistent with levels reported in adult KICS (Table 1) [1, 3]. As noted in the Methods, there were 2 additional patients from our pilot study evaluating the virologic characteristics of pediatric KS that technically would have fit the case definition for adult KICS [6]. These 2 patients, however, did not present with persistent fevers or hepatosplenomegaly and achieved long-term complete remission with BV alone. Without virologic testing, they would have been clinically categorized as lymphadenopathic KS, and their treatment response correlated with its favorable prognosis. Potentially, there exists a spectrum of severity in the hyperinflammatory response in pediatric KS.

The question of whether the patients without biopsies had MCD rather than KICS is important to consider. MCD, especially when treated with steroids only, exhibits a chronic remitting and relapsing course [2]. Long-term follow-up without recurrence in the 4 survivors would be uncharacteristic for MCD, and is consistent with reports of adult KICS survivors [1–3].

The clinical features described here are also similar to HLH, which can occur secondary to viral infection or malignancy [10, 13]. Although KS is rarely associated with HLH, 5 HIV-infected adults with KSHV-associated HLH were reported from France (3 being African immigrants) prior to the initial description of KICS, demonstrating similar clinical features [14]. Due to limitations in resources, we could not distinguish these entities. It is plausible that there exists overlap between KICS and HLH. Future studies are needed to systematically define the mechanisms of immune dysregulation underlying KICS. If KICS represents a form of HLH, immunosuppression may be critical to minimize complications from uncontrolled inflammation [13].

Challenges inherent to working in an environment with limited medical resources are important to consider, including constraints on obtaining biopsies and comprehensive laboratory analyses. Ultimately, this report lends evidence that KICS occurs in HIV-infected children living in KSHV-endemic regions of Africa. Increased awareness of KSHV-associated disorders is indicated as the disease biology and therapeutic strategies continue to be defined.

Notes

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