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Navigating the heterogeneous landscape of pediatric Kaposi sarcoma

William Kamiyango[1,2] · Jimmy Villiera[1,2] · Allison Silverstein[1,2,3] · Erin Peckham-Gregory[3,4] · Liane R. Campbell[3,5] · Nader Kim El-Mallawany[3,4]

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Abstract

Vivid descriptions of Kaposi sarcoma (KS) occurring in children and adolescents from central and eastern Africa originated over 50 years ago. Unique clinical characteristics of pediatric KS in Africa were well described within these geographic regions that were eventually understood to be endemic for human herpesvirus-8/Kaposi sarcoma herpesvirus (HHV-8/KSHV) infection, the causative agent of KS. Having catapulted in incidence with the HIV epidemic, KS is currently among the top five most common childhood cancers in numerous countries throughout the region. The main feature that differentiates the childhood form of KS from adult disease is clinical presentation with primarily bulging lymphadenopathy. This group of patients represents the most common clinical subtype of pediatric KS in KSHV-endemic regions. Lymphadenopathic KS in children is associated with other distinct features, such as sparse occurrence of prototypical hyperpigmented cutaneous lesions, frequent presentation with severe cytopenias and a normal CD4 count, and a fulminant clinical course if untreated with chemotherapy. Increased awareness and improved recognition of lymphadenopathic KS are critically important, particularly because this subset of patients typically experiences a favorable response to chemotherapy characterized by durable complete remission. Clinical phenotypes typically observed in adult KS also occur in children—mild/moderate disease limited to cutaneous and oral involvement, woody edema, and visceral disease. This review summarizes the heterogeneous patterns of disease presentation and treatment response observed among the divergent clinical phenotypes of pediatric KS, highlights additional KSHV-related malignancies, and explores some of the potential biological drivers of such clinical phenomena.

Keywords Kaposi sarcoma (KS) · Human herpesvirus-8 (HHV-8) · Kaposi sarcoma associated herpesvirus (KSHV) · Pediatric oncology · Global health · HIV

1 Introduction

Kaposi sarcoma (KS) rose to prominence as an epidemic in the USA in the early 1980s with the onset of HIV [1]. Prototypical cases of KS were described in adult patients with acquired immunodeficiency syndrome presenting with hyperpigmented cutaneous lesions, edema, involvement of the oral mucosa, and visceral disease [2, 3]. As cancer so rarely arises in the form of an epidemic, the cause of KS was extensively investigated, ultimately leading to the discovery of human herpesvirus-8 (HHV-8)/KS-associated herpesvirus (KSHV) as its etiologic agent in 1994 [4].

The endemic variant of KS however, occurring in both children and adults in Africa, long preceded the HIV epidemic; original descriptions date back as early as the 1950s [5, 6]. The epidemiology of endemic KS is plausibly linked to the worldwide geographic variation of its causative agent, KSHV [7, 8]. While KSHV seroprevalence rates are significantly higher in sub-Saharan Africa compared with the rest of the world, even within Africa, KSHV prevalence and the epidemiological pattern of endemic KS vary [7–14]. Eastern and central Africa have the highest rates of childhood KSHV infection in the world; understandably, this region has been the epicenter of pediatric KS for over 50 years [15].

William Kamiyango and Jimmy Villiera contributed equally to this work.

✉ Nader Kim El-Mallawany
nader.el-mallawany@bcm.edu

[1] Baylor College of Medicine Children's Foundation Malawi, Lilongwe, Malawi

[2] Texas Children's Cancer and Hematology Centers Global HOPE Program, Lilongwe, Malawi

[3] Baylor College of Medicine, Houston, TX, USA

[4] Global HOPE (Hematology-Oncology Pediatric Excellence), Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, 1102 Bates Street, Feigin Tower, Room 1025.16, Houston, TX 77030, USA

[5] Baylor College of Medicine Children's Foundation Tanzania, Mbeya, Tanzania

Endemic KS has long been an important entity in cancer epidemiology in sub-Saharan Africa [16]. With continued devastation caused by the HIV epidemic, the overlap of HIV-related and endemic HIV-negative KS in KSHV-endemic regions has propelled KS to one of the most common childhood cancers in eastern, central, and southern Africa [17–23]. And despite the continued rollout of ART to children and adults across the continent, both HIV-related and endemic KS continue to be prominent [16, 24, 25]. In stark contrast to the existing burden of KS among KSHV-endemic regions in Africa, pediatric KS was a rare occurrence in the USA and Europe in the pre-combination antiretroviral therapy (ART) era [26–31]. Additionally, classical and transplant-associated KS in children are extremely rare entities; therefore, discussions of pediatric KS primarily focus on the endemic and HIV-related epidemiological variants in Africa [32]. As health systems infrastructure continues to make progress in sub-Saharan Africa, including continued efforts to care for children with HIV infection as well as dedicated efforts towards scaling up oncology services, recognition of the clinical features and optimal treatment strategies for pediatric KS will be important in improving overall outcomes across the region [15, 33]. In this review, we discuss the distinct features of pediatric KS occurring in sub-Saharan Africa, the heterogeneous nature of the varying clinical phenotypes, KSHV-related malignancies, and potential underlying biological factors driving these phenomena.

2 Distinct clinical features of childhood KS

Detailed clinical descriptions of pediatric KS from Uganda and Tanzania from 40 to 50 years ago originally identified features that distinguished childhood disease from the adult form [6, 34]. Prototypical characteristics of adult KS include clinical presentation with mucocutaneous involvement, woody edema, and visceral disease [2, 3]. In early reports of childhood KS, Olweny et al. helped define critical distinctions between the pediatric and adult forms of disease; such unique features included clinical presentation with primarily bulging lymphadenopathy, sparsely distributed skin lesions, and a fulminating clinical course if untreated with chemotherapy (Table 1) [34].

The contemporary experience caring for children with both HIV-related and endemic KS has re-affirmed the original descriptions resoundingly [15]. Reviewing published data on pediatric KS over a time period of 50 years, clinical presentation with lymph node involvement (typically ranging from 50 to 90% of cohorts) and lower than theoretically expected proportions of patients with prototypical cutaneous lesions (typically ranging from 45 to 60% of cohorts) have been consistently demonstrated [6, 15, 34–41]. Additional distinct features of childhood KS that have been reported in the contemporary HIV epidemic era include frequent clinical presentation with severe thrombocytopenia, severe anemia, and a normal CD4 count, as well as the rarity of disease regression with ART alone, i.e., without the addition of chemotherapy (Table 1) [15, 36, 38–42].

The cytopenias associated with pediatric KS deserve special mention, as this phenomenon is associated with numerous clinical dilemmas. The typical scenario involves a young child with primarily lymphadenopathic KS presenting with moderate-severe anemia and/or moderate-severe thrombocytopenia. These cytopenias are a relatively frequent occurrence, with 25–37% of cohorts presenting with a hemoglobin < 8 g/dL, and 25–29% of patients presenting with a platelet count < 100×10^9/L [38–41]. Severity of the cytopenias can be life-threatening, with patients presenting with hemoglobin levels as low as 4 g/dL and platelet counts less than 10×10^9/L. In such scenarios, especially in settings where platelet transfusions are not readily available, diagnostic biopsies are often infeasible due to the risk of bleeding complications. This can not only lead to delayed diagnoses but also, even worse, result in death before chemotherapy is initiated in patients who present acutely with the fulminant disease process described in association with lymphadenopathic KS. The authors have experienced such devastating clinical scenarios in the early days of their pediatric KS programs and therefore strongly advocate for having a high index of suspicion for a diagnosis of lymphadenopathic KS in HIV-infected children presenting with bulging lymphadenopathy and severe cytopenias. It is important to note that these cytopenias typically improve rapidly after initiation of chemotherapy, sometimes within a few days, and nearly 90% of patients who present with severe thrombocytopenia will achieve a normal platelet count within 2 weeks of initiating chemotherapy, even in the absence of platelet transfusion [40]. Therefore, it is critical to understand that the initiation of chemotherapy must *not* be delayed in the setting of severe cytopenias. Although bone marrow biopsies have not been routinely performed on pediatric KS patients presenting with cytopenias, it is hypothesized that the cytopenias occur secondary to bone marrow suppression arising in a setting of systemic inflammation, as has been described in analogous clinical settings of patients with multicentric Castleman disease (MCD) and the KSHV inflammatory cytokine syndrome (KICS), both of which are described in further detail later [43–45].

3 Clinical heterogeneity in pediatric KS

The subset of patients with primarily lymphadenopathic KS is associated with these aforementioned distinct clinical features of childhood KS—including the sparse presence of prototypical cutaneous lesions, presentation with severe cytopenias and a preserved CD4 count, and a fulminant clinical course

Table 1 Distinctions and similarities between pediatric and adult Kaposi sarcoma

Clinical features	KS in children	KS in adults
Lymph node involvement	Predominance of primarily lymph node involvement	Lymph node involvement less common, less prominent
Cutaneous lesions	Sparse and anomalous cutaneous involvement	Present in vast majority of patients
	Poor prognosis of disseminated/widespread skin disease	Number of skin lesions not necessarily prognostic
	Uncommon occurrence of mild mucocutaneous disease	
Woody edema	Chronic, indolent nature of woody edema, associated with older age in pediatrics (adolescence)	
Visceral disease	Worse prognosis for patients with visceral disease	
Laboratory findings	Presentation with severe thrombocytopenia and anemia	Thrombocytopenia is exceedingly rare
	Commonly presents with normal CD4 count	Association with severe CD4 count suppression
Treatment	Virtually all patients require chemotherapy plus ART	Some patients will respond to ART alone
Clinical course	Fulminant clinical course in lymphadenopathic KS	More often exhibits indolent clinical course

KS Kaposi sarcoma, *ART* antiretroviral therapy

if the initiation of chemotherapy is delayed [46]. Children with lymphadenopathic KS can present in complete absence of prototypical hyperpigmented skin and oral lesions or woody edema—a phenomenon that has been demonstrated for over five decades [6, 34, 35, 40]. In a contemporary cohort from Malawi, 26% of patients presented with lymphadenopathic KS without other prototypical features [40]. From this same cohort ($n = 70$), analysis of clinical variables associated with outcomes after treatment with bleomycin and vincristine (BV) chemotherapy plus ART demonstrated that lymph node involvement—particularly the lymph node only presentation—was associated with lower mortality risk and lower risk for failure to achieve event-free survival (EFS) [40]. Ultimately, it appears that this unique subset of children with lymphadenopathic KS, the most common clinical presentation of KS in children living in KSHV-endemic regions, represents the major distinction between pediatric and adult disease (Fig. 1).

Although the authors place great emphasis on the important phenomenon of lymphadenopathic KS in children, it must be noted that prototypical clinical phenotypes that are more representative of adult KS do also occur. Clinical presentation with cutaneous lesions, oral mucosal involvement, woody edema, and visceral disease has also been observed in children and adolescents with KS [15]. In KSHV-endemic regions, there appears to be a heterogeneous mosaic of distinct patterns of clinical presentation and treatment response [15, 46]. Multivariate analysis of clinical variables associated with survival outcomes has demonstrated that visceral disease and/or disseminated/widespread cutaneous involvement were significantly associated with increased risk of death and failure to achieve EFS, while presentation with woody edema was associated with increased risk of failure to achieve EFS without increased mortality risk [40]. Divergent treatment outcomes associated with these phenotypically distinct subsets of patients served as the basis for devising a pediatric-specific KS

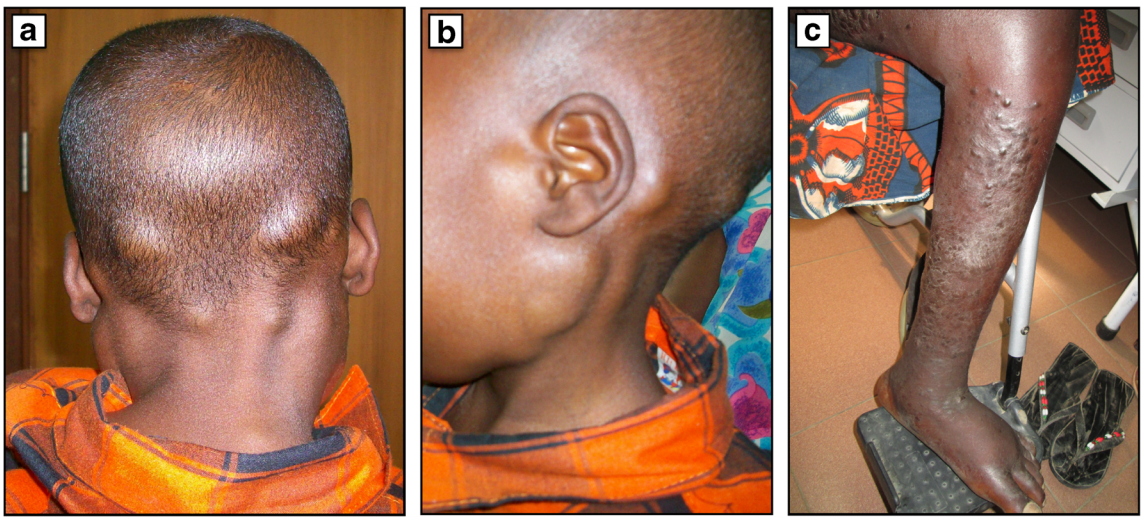

Fig. 1 Photographic representation of the typical bulging lymphadenopathy in a child with lymphadenopathic Kaposi sarcoma (**a**, **b**), as well as a patient with woody edema of the lower extremity (**c**). These photographs were obtained and used for publication with the written consent of parental guardians

staging classification in an attempt to address the unique clinical patterns observed in KSHV-endemic regions of Africa [15, 46].

The Lilongwe Pediatric KS Staging Classification stratifies four distinct groups (termed stages) based on clinical phenotype: (1) mild/moderate disease limited to cutaneous and oral mucosal involvement, (2) lymphadenopathic disease, (3) woody edema (Fig. 1), and (4) visceral and/or disseminated cutaneous/oral disease [15]. It is important to note some nuanced details of the staging classification. For example, disseminated skin disease is defined as having greater than or equal to 20 hyperpigmented skin/oral lesions in widespread distribution, thereby excluding flesh-colored subcutaneous nodules as well as establishing the caveat that coalescing or confluent hyperpigmented skin lesions localized to a single anatomic region only count as a single lesion per cluster. Additionally, patients can only be up-staged; for example, children with lymph node and visceral lung involvement would be categorized as stage 4 visceral disease and not stage 2 lymphadenopathic disease [15].

By grouping these four clinical phenotypes into distinct staging categories, we have attempted to stratify patients based on divergent treatment outcomes (Table 2). Mild/moderate disease limited to cutaneous/oral involvement (stage 1) appears to be an uncommon occurrence in African children with KS, representing approximately 5–8% of cohorts [15]. It has been difficult to define the clinical characteristics associated with this subset of patients due to small sample sizes. This group of patients may represent a subset that could potentially be treated with ART alone and spared chemotherapy; however, this remains to be determined [15]. The authors caution though that in their anecdotal experience treating children with KS in Malawi and Tanzania, most patients with mild/moderate cutaneous/oral disease required chemotherapy in addition to ART. As previously mentioned, lymphadenopathic KS (stage 2) is the most common clinical phenotype of pediatric KS occurring in KSHV-endemic regions. It is associated with younger age, frequent occurrence of severe cytopenias, presentation without prototypical skin/oral/edematous lesions, and a fulminant clinical course if chemotherapy is not promptly initiated. Nevertheless, lymphadenopathic KS has a favorable prognosis when treated with the mild/moderate BV chemotherapy regimen, and the vast majority of patients achieve long-standing durable complete remission (CR) [15, 46]. Contrastingly, woody edema KS (stage 3) is associated with older age, typically occurring in teenagers. It has an indolent clinical course, whereby CR is rarely achieved and most patients live on with stable disease after treatment with chemotherapy plus ART, but with low mortality rates [15, 46]. Patients with visceral and/or disseminated skin/oral involvement (stage 4) represent the highest-risk group with the worst survival outcomes when treated with BV chemotherapy. There is no age predilection for this subset of patients; they often present with severely low CD4 counts and experience high rates of disease relapse and KS-related mortality [15, 46]. It is notable that while adults with KS frequently present with innumerable skin lesions (even in the 50–100 range) without negative prognostic association, presenting with such widespread skin involvement in children is associated with increased risk of death and failure to achieve EFS in multivariate analysis, independent of visceral involvement [40].

Patterns of death based upon the Lilongwe Pediatric KS Staging Classification also reveal a telling story. Combining the published experience with both HIV-related and endemic HIV-negative pediatric KS from Lilongwe, Malawi, demonstrates contrasting mortality patterns (Table 3). Of the 18 patients with stage 4 visceral/disseminated KS who died, all 18 experienced KS-related deaths in the context of relapsed/refractory disease that progressed [46, 47]. Of the ten patients

Table 2 Distinct patterns of disease presentation stratify according to clinical staging categories

	Stage 1	Stage 2	Stage 3	Stage 4
Clinical phenotype	Mild/moderate KS, limited to skin and oral mucosa	Lymph node	Woody edema	Visceral and/or disseminated skin/oral
Distinct characteristic features	Rare occurrence	Often younger children	Often teenagers	No age predilection
	Mild KS may respond to ART?	Can occur without skin lesions	Indolent clinical course	Often with severely low CD4
	Moderate KS needs chemo	Frequent cytopenias	Cytopenias rare	Frequent cytopenias
	Usually achieve CR	Deadly without chemo	Rarely achieve CR	High rates of relapse
		Usually achieve CR	Low mortality	High KS-related mortality
Event-free survival	High	High	Low	Low
Overall survival	High	High	High	Low
Treatment	ART +/− chemo	chemo + ART	chemo + ART	intensified chemo + ART

KS Kaposi sarcoma, *ART* antiretroviral therapy, *CR* complete remission, *chemo* chemotherapy

Table 3 Causes of death in context of the Lilongwe pediatric Kaposi sarcoma staging classification

	Time point (from date of KS diagnosis)							
	< 1 month		1–6 months		> 6 months		Totals	
	Cause of death: KS versus non-KS							
	KS	Non-KS	KS	Non-KS	KS	Non-KS	KS	Non-KS
Stage 1, mild/moderate skin/oral KS	0	0	0	1	0	1	0	2
Stage 2, lymphadenopathic KS	4	2	0	1	1	2	5	5
Stage 3, woody edema KS	0	1	0	1	2	2	2	4
Stage 4, visceral/disseminated KS	7	0	8	0	3	0	18	0

KS Kaposi sarcoma

with stage 2 lymphadenopathic KS who died, five were categorized as KS-related and the remainder died of other HIV-related comorbidities, namely infection and severe malnutrition. Of the five KS-related deaths in children with lymphadenopathic disease, four of them occurred at the onset of their KS diagnosis, in the context of delayed initiation of chemotherapy secondary to delays in establishing a definitive diagnosis of lymphadenopathic KS, highlighting the fulminant clinical course experienced by patients who are not promptly treated with chemotherapy [46, 47].

Ultimately, these divergent clinical phenotypes are associated with distinctly different responses to treatment and associated survival outcomes. While definitive outcome data is lacking for patients with stage 1 disease, based on our limited anecdotal experience, these patients have favorable outcomes. For patients categorized as stages 2, 3, and 4 though, outcome patterns have been significantly disparate. Lymphadenopathic KS is associated with favorable EFS and overall survival (OS), woody edema with low EFS but favorable OS, and visceral/disseminated KS with dismal EFS and OS after frontline treatment with BV chemotherapy plus ART (Table 2) [46]. Based on these data, it was apparent that a risk-stratified, response-adapted treatment regimen was needed to optimize the therapeutic approach [15]. The BV regimen has very mild cytotoxicity, is rarely associated with severe chemotherapy-induced cytopenias, is widely accessible and affordable, and is therefore the pragmatic choice as a first-line regimen based on its efficacy for patients with stage 1, 2, and 3 diseases [40]. The authors currently reserve intensified first-line chemotherapy for patients with stage 4 disease; intensified regimens are usually based on drug availability, but typically include the addition of conventional doxorubicin to BV, or paclitaxel monotherapy [15, 40]. In a scenario where liposomal doxorubicin is potentially available, this would also serve as an ideal alternative; however, cost often prohibits its availability in low-income settings [48].

4 Comparing endemic and HIV-related pediatric KS

While HIV-related epidemic KS has overshadowed its endemic counterpart over the past 20 years, it is important to recognize that endemic disease was still among the most common childhood malignancies in KSHV-endemic regions prior to the HIV epidemic [16]. Comparisons of endemic and HIV-related pediatric KS have revealed overlapping similarities with subtle nuanced distinctions (Table 4) [47]. Importantly, for both epidemiological variants, lymphadenopathic disease is prominent, prototypical skin lesions are often absent, cytopenias occur with similar frequency, and treatment outcomes are ultimately similar [47]. As previously mentioned, treatment outcomes for children with KS appear to stratify based on their clinical phenotype (i.e., the Lilongwe Pediatric Staging Classification) and do not appear to differ based on the epidemiological variant [47]. In a cohort of 20 children with endemic KS from Malawi, of the ten patients categorized as stages 1 and 2, eight were alive and in CR. On the other hand, among six patients with stage 3 disease, there was one CR, three were alive with stable disease, and two experienced multiple relapses and eventually died of progressive disease. The four patients categorized as stage 4 were all based on disseminated cutaneous involvement in the absence of visceral disease; three patients experienced disease progression despite intensified treatment with doxorubicin plus BV and all three died from their underlying KS [47].

5 Other KSHV-associated malignancies

Although KS is the most common malignancy associated with KSHV, it is important to consider other KSHV-related malignancies in regions where KSHV is endemic, and HIV prevalence rates remain high. Other diseases associated with KSHV include MCD, KICS, primary effusion lymphoma (PEL), diffuse large B cell lymphoma arising in the setting of MCD, and

Table 4 Comparing endemic HIV-negative and HIV-related pediatric Kaposi sarcoma

Endemic, HIV-negative KS	**Epidemic, HIV-related KS**
Features shared in common	
Similar treatment outcomes	
Prominence of lymph node involvement	
Frequent presentation with severe thrombocytopenia & anemia	
Prototypical cutaneous lesions often absent	
Distinctions between endemic and epidemic KS	
Lower proportion with oral involvement	Higher proportion with visceral involvement
Treatment with chemotherapy only	Treatment with chemotherapy plus ART

KS Kaposi sarcoma, *ART* antiretroviral therapy

germinotrophic lymphoproliferative disorder [49–51]. In particular, although MCD, KICS, and PEL are relatively uncommon HIV-related malignancies, they can all present concurrent with KS and with clinical features that may be overlapping [50, 51].

KSHV-associated MCD is a lymphoproliferative disorder that typically occurs in the setting of immunosuppression from underlying HIV infection [51, 52]. Patients typically present with features of systemic inflammation including fevers, multifocal lymphadenopathy, splenomegaly, and cytopenias [52]. The common occurrence of lymphadenopathy and cytopenias in children with KS renders the diagnostic distinction between MCD and lymphadenopathic KS critical. Clinically though, KS does not typically present with features of systemic inflammation (i.e., fevers and organomegaly), which when present should raise suspicion for MCD or KICS. Although definitive diagnosis of MCD may be limited by available pathology resources and expertise in KSHV-endemic regions of Africa, continued development of the Pathology Laboratory at Kamuzu Central Hospital in Malawi has led to the identification of numerous cases of KSHV-associated MCD in adults [53, 54]. Recent publication of a cohort of 22 HIV-infected adult patients with KSHV-associated MCD has established important precedent, highlighting not only disease incidence but also the value of comprehensive pathology services [55]. While MCD has yet to be reported in pediatric patients from KSHV-endemic regions, we hypothesize that this is more likely due to regional limitations in pathology services.

KICS is a recently described KSHV-related disorder that shares clinical and virologic overlap with MCD [44, 50, 51, 56]. Both are characterized by clinical presentation with a hyperinflammatory syndrome and virologic features of KSHV lytic activation represented by extreme elevations of KSHV viral load and cytokines such as interleukin (IL)-6 and IL-10 [56, 57]. Viral IL-6 is a KSHV-specific viral antigen and a homolog to human IL-6 [58]. Its expression and subsequently the expression of human IL-6 as well are elevated in the setting of KSHV lytic activation [56–58]. In descriptions of HIV-infected adults with KICS, patients typically presented with KS and features of systemic inflammation in the absence of histologic evidence of MCD [44, 45]. A minority of patients with KICS presented in the context of a diagnosis of PEL [45].

A cohort of children with KICS was recently reported from Lilongwe, Malawi. Seven patients presented with typical features of lymphadenopathic KS, namely bulging lymphadenopathy and severe thrombocytopenia and anemia; however, the presence of persistent high fevers and massive hepatosplenomegaly extending to the level of the umbilicus/pelvis distinguished their clinical presentation [59]. In comparing these children with KICS with the historical pediatric KS cohorts, and specifically the subset with lymphadenopathic KS, children with KICS were younger (median age 3.5 years) and with more severe cytopenias (median platelet count 14×10^9/L and median hemoglobin 4.8 g/dL) [59]. Those patients who had biopsies performed demonstrated histology definitive for lymphadenopathic KS without evidence of MCD. Through collaborative efforts with the University of North Carolina Vironomics Laboratory, virologic analyses were obtained on two patients, both of whom demonstrated extreme elevations of KSHV viral load, IL-6, and IL-10 levels in plasma [59]. Clinically, unlike the typical course for patients with lymphadenopathic KS, these children with KICS did not demonstrate rapid improvement after initiation of BV chemotherapy. In the absence of more sophisticated therapeutic options for KICS (i.e., rituximab or anti-IL-6 agents), prednisone was added to the BV regimen. Although three of the seven children experienced early death, deteriorating quickly after presentation with multi-organ failure, four patients went on to achieve complete remission with a median follow-up of 44 months (range 31–50). Notably, within 2 weeks of initiating prednisone plus BV, the median platelet count increased from 14 to 587×10^9/L, in the absence of transfusion, reflecting the dramatic response to treatment of both the hyperinflammatory syndrome in addition to the underlying KS [59].

Finally, PEL is another KSHV-associated malignancy deserving further recognition due to its clinical similarity to pulmonary KS. Patients typically present with massive effusions in the pleural, peritoneal, or pericardial cavities [60, 61].

Although its occurrence has not been documented in KSHV-endemic regions of Africa, the extracavitary variant of PEL has been reported in HIV-infected adults from Malawi [62]. Similar to MCD, PEL can present concurrently with KS, and differentiating pulmonary KS from PEL can be extremely challenging, particularly with the paucity of pathology resources available in the region [50, 51, 60, 61]. Pleural effusions in patients with pulmonary KS should not manifest evidence of malignant cells on cytology analyses, while those of patients with PEL typically do. However, establishing a definitive diagnosis based on cytology alone requires extensive expertise that few pathologists in the world can provide [61]. Therefore, more sophisticated diagnostic methods could potentially be enlightening, specifically flow cytometry or even quantitative analysis of KSHV viral load from the effusion fluid [61, 63].

6 Potential biological phenomena driving distinct clinical phenotypes

KSHV lytic activation—manifested by elevations of KSHV viral load, IL-6, and IL-10 levels—is an essential biological feature of the mechanisms of viral oncogenesis in KICS and MCD. Considering the clinical overlap between children with lymphadenopathic KS and the presentations of KICS and MCD, the authors have hypothesized that similar mechanisms of viral pathophysiology may be driving the clinical features of lymphadenopathic KS. In a pilot study evaluating the virologic characteristics of pediatric KS in Malawi, two-thirds of the cohort had KSHV viremia at the time of KS diagnosis and 39% of patients had a human IL-6 level greater than two times the upper limit of normal. The median IL-10 of 19.53 pg/mL was nearly four times the upper limit of normal [64]. Evaluating virologic findings with clinical characteristics, KSHV viremia was significantly associated with clinical presentation with lymphadenopathy ($p = 0.004$) as well as categorization by pediatric KS staging classification ($p = 0.001$) [64]. All of the patients with KSHV viremia were categorized as either stage 2 lymphadenopathic KS or stage 4 visceral/disseminated skin/oral disease, while all patients categorized as stage 1 mild/moderate skin/oral disease or stage 3 woody edema KS presented with undetectable KSHV viral loads [64].

In addition to the clinical heterogeneity observed in pediatric KS, there appears to be heterogeneity of virologic characteristics that may be causally linked. Results from this pilot study will need to be validated in a larger cohort, but it is notable that similar precedent has been established in adult KS patients from Malawi [65]. In a study evaluating the KSHV transcription profile of KS in Malawian adults, two distinct subtypes were demonstrated: (1) lesions that—similar to adult KS from the USA—displayed only limited transcription restricted to the latency locus and (2) lesions that exhibited more lytic phase features through transcription of viral RNAs across the length of the KSHV viral genome [65]. Ultimately, the authors conceive the heterogeneity of KSHV-related malignancies and disease presentations as existing along a spectrum of KSHV virologic activity (Fig. 2). On the one end of the spectrum, latent phase KSHV is linked with mild mucocutaneous and woody edema KS, while on the other, lytic phase activation of KSHV represented by extreme KSHV viremia and elevations of associated cytokines is associated with KICS and MCD. Somewhere along this spectrum of lytic phase KSHV activation lies lymphadenopathic KS of childhood, and potentially as well, the severe phenotypes of KS such as visceral or disseminated mucocutaneous disease. Continued investigation of the clinical patterns of KS in Africa and their associated biological characteristics may shed light on mechanisms of disease pathogenesis and hopefully enhanced therapeutic options.

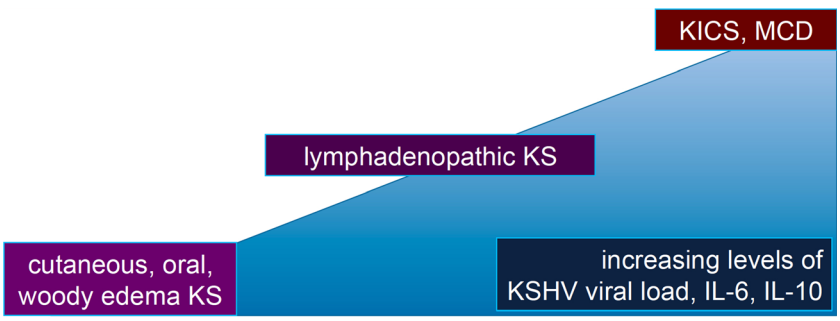

Fig. 2 The spectrum of virologic activity of Kaposi sarcoma–associated herpesvirus (KSHV), ranging from latent phase and its association with mild Kaposi sarcoma (KS) to KSHV lytic activation and its association with KSHV inflammatory cytokine syndrome (KICS) and multicentric Castleman disease (MCD) characterized by extreme elevations in the KSHV viral load, interleukin (IL)-6, and IL-10 levels. Lymphadenopathic KS of childhood appears to lie somewhere along this spectrum of KSHV lytic activation

7 Conclusions

Since early KS descriptions over 50 years ago, characterization of distinct childhood features of KS has helped to lay foundations for enhanced knowledge of the disease as well as improved care and outcomes for patients. Specifically, in this review, we highlight the clinical presentation of lymphadenopathic KS in children that is unique from the prototypical adult presentations. For both HIV-related and endemic HIV-negative pediatric KS, there exists distinct clinical heterogeneity in disease presentation and response to treatment. Recognizing the clinical patterns is a critical first step to determining the optimal therapeutic approach based on risk-stratification according to prognosis. The authors advocate for a risk-stratified, response-adapted treatment regimen that stratifies all children with KS, regardless of their HIV serostatus, based upon categorization of their clinical phenotype [15]. Other KSHV-related malignancies must also be recognized, as they may have overlapping features with KS and warrant specific consideration and possibly unique approaches to care. Further, KSHV lytic activation—as evident by elevations of KSHV viral load, IL-6, and IL-10—may help provide further clarity to distinguish clinical phenotypes. Through collaborative, international efforts, we hope to definitively establish the safest, most effective treatment approaches and continue to improve survival outcomes for children with KS in sub-Saharan Africa and beyond.

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Compliance with ethical standards

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