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Kaposi sarcoma of childhood: inborn or acquired immunodeficiency to oncogenic HHV-8

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Abstract

Kaposi sarcoma (KS) is an endothelial malignancy caused by human herpes virus-8 (HHV-8) infection. The epidemic and iatrogenic forms of childhood KS result from a profound and acquired T cell deficiency. Recent studies have shown that classic KS of childhood can result from rare single-gene inborn errors of immunity, with mutations in *WAS*, *IFNGR1*, *STIM1*, and *TNFRSF4*. The pathogenesis of the endemic form of childhood KS has remained elusive. We review childhood KS pathogenesis and its relationship to inherited and acquired immunodeficiency to oncogenic HHV-8.

Keywords

Kaposi sarcoma; human herpes virus-8; HHV-8; pediatric; children

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Conflict of Interests

The authors have no conflict of interests to declare.

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Introduction

Kaposi sarcoma (KS) is an inflammatory neoplasm of endothelial cell origin first defined by Hungarian dermatologist, Moritz Kaposi in 1872 [1]. KS is probably a polyclonal proliferation of spindle cell latently infected by human herpes virus-8 (HHV-8), which often evolves into an oligoclonal/monoclonal disorder [2-4]. It is currently classified under four epidemiologic forms [5]. *Classic* KS primarily affects elderly men mostly over 60 years old of Eastern European and Mediterranean origin, typically presenting with indolent and chronic cutaneous plaques and nodules. *Endemic* KS in Sub-Saharan Africa affects younger adults, with a rapidly progressive lymphadenopathic course. *Epidemic* KS in human immunodeficiency virus- (HIV-) infected and acquired immune deficiency syndrome (AIDS) patients and *iatrogenic* KS in medically immunosuppressed (e.g. transplanted) patients, typically follow a rapidly progressive course, affecting the skin, mucosae, lymphatic system, and visceral organs. Human herpes virus-8 (HHV-8), also designated as KS-associated herpes virus (KSHV), is the causative agent for all epidemiological forms of KS in all patients [6]. The vast majority of HHV-8 infected individuals (more than 40% individuals in some populations, based on seroprevalence) do not develop KS [7]. This virus can cause at least two other conditions, some forms of multicentric Castleman's disease and primary effusion lymphoma, both of which can however occur in the absence of HHV-8 infection [8].

The prevalence of HHV-8 varies globally, with high-level of more than 40% seropositivity in parts of Africa and South America, intermediate level of 30-40% seropositivity in the Mediterranean, and low levels of up to 20% seropositivity in non-endemic areas such as North America, Northern Europe, and most of Asia [7]. There exists some major HHV-8 genotypes, many of which are geographically restricted, with little evidence to support whether any genotype is more virulent or more associated with KS [9-13]. In 2009, in addition to Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus-1, Human Papillomaviruses, and Human T-Cell Lymphotropic Virus Type-1, the World Health Organization's International Agency for Research on Cancer declared HHV-8 a Group 1 carcinogenic virus, highlighting its public health significance [14].

In evaluating a patient with KS, a complete physical examination is necessary with evaluation of visceral disease for patients with systemic or organ-specific symptoms. Biopsy of the KS lesion is required for definitive diagnosis. Histologic features include spindle shaped cells, inflammatory infiltrates, and angioproliferation with erythrocyte extravasation. Endothelial cell markers (CD31, CD34, factor VIII) and lymphatic endothelial cell markers (lymphatic vessel endothelial receptor 1), are oftentimes useful to support the diagnosis of KS [15]. However, detection of HHV-8 latency-associated nuclear antigen (LANA), expressed in all clinical stages of KS, in spindle cells, which are the proliferating HHV-8-infected endothelial cells, is a more definitive histologic diagnosis [15-17]. AIDS-associated KS is staged according the classification developed by the AIDS Clinical Trials Group (ACTG) Oncology Committee which stratifies patients based on tumor burden, immune status, and presence of any systemic symptoms [18]. There is no validated staging system for the other epidemiologic forms of KS (classic, endemic, and iatrogenic).

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For patients with epidemic or iatrogenic KS, the most effective treatment requires correcting the underlying immunodeficiency. The prognosis of epidemic KS has greatly improved with the use of highly active anti-retroviral therapies (HAART). However KS remains the most common AIDS-associated malignancy worldwide and the common form of all cancers in adult males and the second or third most common cancer in women and children in many parts of sub-Saharan Africa where HAART is not widely available [19,20], posing a significant burden on human health worldwide. There is evidence that patients with iatrogenic KS, specifically those with renal transplants under cyclosporine immunosuppression, have had tumor regression when immunosuppression was switched to sirolimus, a mammalian target of rapamycin (mTOR) inhibitor sharing both immunosuppressive and anti-neoplastic effects [21,22]. Treatment for endemic and classic forms of KS are targeted on the basis of localized or disseminated disease. Symptomatic localized lesions are oftentimes treated with local measures such as intralesional vinblastine, liquid nitrogen, laser therapy, localized radiotherapy, topical retinoic acid, or surgical resection. For patients with multifocal, symptomatic, or disseminated disease requiring systemic therapy, liposomal doxorubicin or liposomal daunorubicin is the first line of choice [23] followed by paclitaxel as second-line treatment [24]. Other modalities with activity against KS include vincristine, vinblastine, vinorelbine, bleomycin, and etoposide. Immunomodulation approaches, such as interferon-α have been evaluated, with promising activity in limited disease in epidemic KS [25].

KS in adults and HHV-8 infection in children have been subjects of recent reviews [8,26]. There is however no review focused on pediatric KS. We will herein review childhood KS, our current understanding of all the epidemiological forms, risk factors for KS development, as well as current treatment approaches. In particular, we will discuss childhood KS pathogenesis and its relationship to inherited and acquired immunodeficiency.

Childhood KS

Epidemiology

Epidemic and Endemic KS—Pediatric KS (summarized in Table 1) is rare, but the prevalence greatly changes within regions of the world where HIV infection is widespread. Prior to the AIDS pandemic, the most frequent form of KS in children was the endemic KS in Africa. However, the insurgence of the AIDS pandemic has increased the incidence of pediatric KS by more than 40-fold, now making epidemic KS the most common form of pediatric KS worldwide [27-29]. In a study of 18 Sub-Saharan African countries, KS was the most common or second most common childhood cancer in many areas of Southern and Eastern Africa, with rates as high as 22% of all pediatric cancers in Uganda [30]. In a study conducted in Africa, HIV positive individuals have 47 times higher odds of KS development compared with the general population [31]; however, specific pediatric data are lacking. Furthermore, there is a paucity of literature on the epidemiology and pathogenesis of endemic (HIV negative) KS as a whole, in both the pre and post HIV pandemic era. In Sub-Saharan Africa, the proportion of endemic KS is estimated to be 36% (266 of 726 KS cases in Zambia confirmed by pathologists were HIV negative) [32]; and that of pediatric endemic

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KS is estimated to be 11% (10 of 92 children in Malawi) [20]. The risk factors for endemic KS, and whether the incidence and prevalence is stable or increasing, are unknown.

Classic and Iatrogenic KS—Pediatric classic and iatrogenic KS are extremely rare, despite the high seroprevalence of HHV-8 in certain regions of the world. In the Mediterranean Basin and certain African regions, seroprevalence can reach 50% in children older than 6 years [33,34], and there is evidence for strong familial aggregation between mother-child and sibling-sibling relationships [35,36]. Classic KS in children is exceedingly rare, with less than 50 reported cases of classic KS in the last 50 years [37-50] (Supplementary Table 1). This corresponds to probably less than 1 case per million infected children. The epidemiology of HHV-8 infection and development of iatrogenic KS in the pediatric population has not yet been fully elucidated. However, data from adult patients with iatrogenic KS after solid organ transplantation indicates a cumulative risk range as low as 0.4% in North America to as high as 6% in regions of the Mediterranean and Middle East, a risk 1000-fold greater than non-transplanted patients [26,51].

Transmission of HHV-8—Horizontal transmission in infancy and childhood is thought to occur primarily through saliva exchange [36,52]. Whereas vertical transmission of HHV-8 have been reported, it is rare and estimated with an incidence of 2% [53]. Interestingly, breast milk transmission has not yet been reported despite the presence of HHV-8 DNA in breast milk of seropositive mothers [54]. Furthermore, there is evidence of HHV-8 transmission by blood transfusion in regions of the world where HHV-8 is endemic [55].

Clinical course

Epidemic KS in pediatric populations frequently follows a more aggressive course; sometimes without cutaneous involvement, and oftentimes involving mucosa and visceral organs. Children with epidemic KS are young (mean 8.8 years) [20], and KS immune reconstitution inflammatory syndrome (IRIS) can occur up to 20% of children with epidemic KS receiving HAART therapy [56]. Children with endemic KS, tend to be younger (mean 6.6 years) and present with generalized or localized lymphadenopathy with sparse mucosal or skin lesions, if any [20]. Pediatric patients with classic KS (mean 8.3 years) present with more rapidly progressive disseminated and aggressive cutaneous lesions, oftentimes with mucosal and lymph node involvement, and can be lethal within 1 to 2 years of presentation (Supplementary Table 1) [41,45]. Pediatric patients with iatrogenic KS are of variable ages depending on the time of immunosuppressive therapy post transplantation. The presentation of pediatric iatrogenic (post transplant) KS is variable, ranging from pancytopenia and lymphadenopathy to more widespread visceral or mucocutaneous-cutaneous involvement [57-61]. In summary, pediatric KS, most common in developing countries, tends to be more aggressive with high mortality, even in HIV negative patients, compared to adult KS [29].

Primary infection with HHV-8 has been documented in the general population in children between 24-36 months of age, and they present with non-specific fever and craniocaudal maculopapupular rash, but not KS [62]. In contrast, primary HHV-8 infection in immunocompromised patients (albeit adults) post transplantation present more aggressively

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with pancytopenia and disseminated lymphadenopathy, and even concomitant KS with HHV-8 seroconversion [63]. Overall, the observation that most children infected with HHV-8, even upon co-infection by HIV but without AIDS, do not develop KS clearly indicates that infection alone is not sufficient to drive KS and that other factors, such as impaired immunity (whether inherited or acquired), are required.

Outcome and treatment

Due to the rarity of pediatric KS, there is a paucity of literature on treatment and outcome stratification, with most treatment modalities options extracted from literature of adults treated for KS. To date, there are no established consensus group therapeutic guidelines for the treatment of all 4 forms (epidemic, endemic, iatrogenic, classic) of pediatric KS. Antiviral therapy (gangiclovir, valganciclovir) can be considered for prevention of (primary) HHV-8 infection and subsequent KS development, with systemic chemotherapy (liposomal doxorubicin, liposomal daunorubicin, paclitaxel, vincristine, etoposide, bleomycin) utilized in cases of pediatric KS with systemic disease, and intralesional chemotherapy (vinblastine, topical retinoic acid) utilized in cases of localized disease [26]. As in adults, the control of HIV and the switch or diminution of immunosuppression is key to the control of epidemic and iatrogenic forms. In cases of epidemic KS, The Cochrane review concluded that chemotherapy and HAART in combination versus HAART alone are more likely associated with KS remission, although data are sparse [64,65]. Children with endemic (African) KS who are HIV negative, oftentimes in resource-limited settings, have better outcomes than those with HIV infection undergoing the same chemotherapeutic regimens [20,56,65-68]. Limited cases of pediatric iatrogenic (liver transplant) KS have shown promising response to mTOR inhibitor sirolimus, and paclitaxel chemotherapy [57,69]. Pediatric classic (Mediterranean) KS, also exceedingly rare with very few case reports, has been treated with various modalities. Three Turkish children with disseminated classic KS had variable responses to systemic chemotherapy: one progressed and died on vincristine, another went into first remission after systemic interferon-α therapy, and a third child progressed despite systemic interferon-α and vinblastine but went into remission after etoposide [45].

Pathogenesis: broad acquired and inborn immunodeficiencies

HHV-8 seropositivity alone does not predict progression to childhood KS, and epidemic and iatrogenic KS attest of an immunodeficiency with greatly increased risk of KS. This suggests that endemic and classic childhood KS may also result from hitherto unknown forms of immunodeficiency, whether inherited or acquired. Human genetic variability may account for phenotypic variability in the clinical outcome of HHV-8 infection. Supporting the hypothesis that inborn errors may account for classic KS predisposition is the identification of children with known inherited immunodeficiencies (i.e. autosomal recessive (AR) interferon-γR1 (IFN-γR1) deficiency, X-linked recessive (XR) Wiskott-Aldrich syndrome) to have either preceding or concurrent KS (Table 2) [44,46]. Interferon-γR1 deficiency is a well-defined primary immunodeficiency that predisposes to mycobacterial disease. There is report of a 10-year child from Turkish consanguineous parents with two copies of C77Y *IFNGR1* null allele, who had low intermittent but persistent $CD4^+$ T cell counts and recurrent disseminated infection caused by Bacille Calmette-Guerin (BCG) vaccine and environmental *Mycobacterium fortuitum* since age of 5 months [44]. He

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concurrently developed aggressive disseminated cutaneous and systemic classic KS confirmed by skin biopsy, and died at 12 years of age of KS progression despite treatment with interferon-α and paclitaxel. Moreover, another report of an 14-month old child with Wiskott-Aldrich syndrome from Tunisian non-consanguineous parents, had a history of multiple bacterial (local infection caused by BCG vaccine, severe staphylococcal pneumonia) and viral infections (Epstein-Barr virus-related lymphoproliferative disease, cytomegalovirus viremia) including HHV-8 infection with aggressive disseminated cutaneous and systemic classic KS confirmed by skin biopsy [46]. The cutaneous KS lesions partially regressed with paclitaxel but complete remission from KS was not obtained until non-T-cell depleted allogeneic hematopoietic stem cell transplant (HSCT). These two cases of classic KS in children with well-described primary immunodeficiency along with the observation of KS remission after HSCT, combined with the comprehension of epidemic and iatrogenic KS pathogenesis, lends further support to the critical role of a functioning immunity against HHV-8 infection and KS development.

Pathogenesis: inborn errors of immunity to HHV-8

Indeed, the first two genetic etiologies of isolated KS (AR STIM1 deficiency and AR OX40 deficiency), both of which impair T cell immunity, were subsequently discovered (Table 2) [70,71]. A 2-year girl born to Turkish consanguineous parents with aggressive disseminated cutaneous and systemic KS died 4 months after presentation from pulmonary lesions. Although the counts and proportions of T, B, and NK cell subsets were normal, she harbored a homozygous splice-site mutation in *STIM1*, leading to primary functional T cell immunodeficiency [70]. Subsequently, a 14-year-old girl born to Turkish consanguineous parents, also with aggressive disseminated cutaneous and systemic classic KS confirmed by skin biopsy, was reported to carry a homozygous R65C null mutant allele in *TNFRSF4* (encoding OX40) [71]. OX40, normally expressed on activated T cells with its ligand (OX40L) expressed on endothelial cells, was lowly expressed on the patient's activated T cell surface with abolition of binding to OX40L. She was treated with interferon-α, vinblastine, and etoposide with subsequent complete remission at last follow-up. These findings provided proof-of-principle that single-gene inborn errors of immunity can underlie aggressive forms of classic KS in childhood. Indeed, there are examples of single-gene inborn errors underlying early-onset cancers [72]. Moreover, isolated childhood infectious diseases, including viral diseases such as herpes simplex encephalitis and severe influenza, can be caused by single-gene immunodeficiencies [73,74]. Epidermodysplasia verruciformis, an autosomal recessive predisposition to papillomavirus-driven non-melanoma skin cancer caused by mutations in EVER1 or EVER2, neatly illustrates both aspects [75-77]. Altogether, the observation of 1) HIV infection with low $CD4^+$ T cell predisposition to epidemic KS, 2) T cell immunosuppression in iatrogenic KS, and 3) T cell impairment in children with classic KS (AR IFN-γR1 deficiency, XR Wiskott-Aldrich syndrome, AR STIM1 deficiency, and AR OX40 deficiency), suggests that HHV-8 exposure alone is insufficient and impaired T cell responses underlie the development of KS. While progress has been made in our understanding of KS-predisposing inborn errors of immunity with the identification of two inborn errors of T cell immunity in two unrelated kindreds [70,71], the genetic etiology of classic KS in children remains largely unexplained. Moreover, the pathogenesis of endemic childhood KS remains unknown. Next generation

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sequencing, with exome and genome sequencing, offers a promising avenue of research in both familial and sporadic cases [78,79].

Concluding remarks

KS continues to cause significant morbidity and mortality worldwide in both pediatric and adult populations. Pediatric KS, in all 4 epidemic forms, is distinct from adult KS, and can be more rapidly progressive with a disseminated course. Indeed, lymph node and mucosal involvement is more common in children, as seen in cases of pediatric classic KS (Supplementary Table 1), despite the fact that classic KS in adults (Supplementary Table 2) are typically limited to indolent cutaneous lesions. Improved therapies for KS are greatly needed, in both resource-limited settings as well as the more-developed world. Immunosuppression from HIV infection and transplantation is associated with higher mortality risks. The known impact of HIV infection, immunosuppression, as well as inborn errors of immunity (mutations in *WAS*, *IFNGR1*, *STIM1*, and *TNFRSF4*) on the development of KS suggest that HHV-8-specific inborn errors of immunity may underlie the pathogenesis of the classic and perhaps even endemic forms of this malignancy in childhood. We aim to bring attention of the pediatric community at large to childhood KS, highlighting that human genetic studies of both classic (Mediterranean) and endemic (African) KS of childhood may provide new directions in understanding the pathogenesis of all epidemiological forms of KS, in children and adults. This may not only be helpful to patients with KS and other HHV-8-related diseases, for diagnosis, prognosis, and therapeutics, but also to patients with other virus-driven cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation Key

KS	Kaposi sarcoma
HHV-8	human herpes virus-8
HIV	human immunodeficiency virus
AIDS	acquired immune deficiency syndrome
KSHV	KS-associated herpes virus
LANA	latency-associated nuclear antigen

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ACTG	AIDS Clinical Trials Group
HAART	highly active anti-retroviral therapies
mTOR	mammalian target of rapamycin
IRIS	immune reconstitution inflammatory syndrome
AR	autosomal recessive
XR	X-linked recessive
BCG	Bacille Calmette-Guerin
HSCT	hematopoietic stem cell transplant
IFN-γR1	interferon-γR1 deficiency

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TABLE I

Four Types of Pediatric Kaposi Sarcoma

Type of KS	Relative Frequency	Geographic Characteristic	Immunodeficiency	Clinical Presentation
Epidemic	Relatively common	Worldwide	AIDS	Aggressive; sometimes without cutaneous involvement, oftentimes involving mucosa and visceral organs, IRIS
Endemic	Rare	Sub-Saharan Africa	Not yet deciphered	Generalized or localized lymphadenopathy with sparse mucosal or skin lesions, if any
Iatrogenic	Very rare	Developed world	Immunosuppressive therapy, (e.g. transplantation)	Variable; lymphadenopathy, visceral, mucocutaneous or cutaneous involvement
Classic	Exceedingly rare	Mediterranean Basin, Eastern European	WAS, IFN-γR1 deficiency, STIM1 deficiency, OX40 deficiency	Rapidly progressive disseminated and aggressive cutaneous lesions, oftentimes with mucosal and lymph node involvement

Abbreviations: KS, Kaposi sarcoma; AIDS, acquired immunodeficiency syndrome; IRIS, immune reconstitution inflammatory syndrome; WAS, Wiskott-Aldrich syndrome

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TABLE II

Genetic Predisposition to Pediatric Kaposi Sarcoma

Gene	Type	Inheritance	PID	Onset age	Presentation	Clinical Outcome
WAS	Classic	XR	Wiskott-Aldrich syndrome	14 months	Aggressive disseminated cutaneous and systemic KS	Complete remission
IFNGR1	Classic	AR	IFN-γRI deficiency	10 years	Aggressive disseminated cutaneous and systemic KS	KS progression and death
STIM1	Classic	AR	STIM1 deficiency	2 years	Aggressive disseminated cutaneous and systemic KS	KS progression and death
TNFRSF4	Classic	AR	OX40 deficiency	14 years	Aggressive disseminated cutaneous and systemic KS	Complete remission

Abbreviations: KS, Kaposi sarcoma; XR, X-linked recessive; AR, autosomal recessive; PID, pediatric immunodeficiency

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