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REVIEW

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Today's Kaposi sarcoma is not the same as it was 40 years ago, or is it?

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Abstract

This review will provide an overview of the notion that Kaposi sarcoma (KS) is a disease that manifests under diverse and divergent circumstances. We begin with a historical introduction of KS and KS-associated herpesvirus (KSHV), highlight the diversity of clinical presentations of KS, summarize what we know about the cell of origin for this tumor, explore KSHV viral load as a potential biomarker for acute KSHV infections and KS-associated complications, and discuss immune modulators that impact KSHV infection, KSHV persistence, and KS disease.

KEYWORDS
herpesvirus, Kaposi sarcoma, KSHV

1 | INTRODUCTION

In 1981 a cluster of Kaposi sarcoma (KS) diagnoses in New York and San Francisco heralded the beginning of the acquired immune deficiency syndrome (AIDS) pandemic.[1] KS was a clinical marker of AIDS before either human immunodeficiency virus (HIV), or KS-associated herpesvirus (KSHV), were discovered. Multifocal lesions, sometimes flat, sometimes nodular, indicated a severe loss of adaptive immune control. At that time, in HIV-uncontrolled AIDS patients, KS lesions occurred at CD4 counts below 200 cells per µL. This manifestation of KSHV infection is commonly referred to as AIDS-KS. AIDS-KS has skin and internal manifestations (Figure 1A—Lung lesion picture). AIDS-KS patients have or had concurrent infections of KSHV with other microorganisms, such as viruses, fungi, or bacteria.

Today, 40 years later, late-stage AIDS KS cases are rarer, but KS remains among the leading cancers in male people living with HIV (PLWH), including those who never developed AIDS and successfully suppressed HIV viral loads.[3–5] This begs the question: is the KS we treat today the same as it was 40 years ago? Is it the same as almost 200 years ago when Moritz Kaposi discovered this disease in HIV-negative, elderly men?

Moritz Kaposi first described KS in 1884 in Vienna, Austria (reviewed in[6]). At the time, Vienna was the most cosmopolitan city on earth. Here, travelers and migrants from across the realm of the Habsburg empire converged. Since 1883 the Orient Express connected Vienna with Constantinople and from there to the Levant, that is, the eastern Mediterranean. Moritz Kaposi was the director of the skin clinic at the Vienna General Hospital. He was among the first to describe xeroderma pigmentosum. At that time, the Vienna General Hospital was the site of the famed Viennese Medical School, where some years earlier, Ignaz Semmelweis formulated basic ideas of hygiene. In broad strokes, one can compare Vienna General Hospital in 1880 with San Francisco General Hospital in 1980: both were centers of clinical excellence where physicians conducted discovery science.

The first case of Sub-Saharan KS was noted in 1960,[7] before the emergence of HIV in the region and shortly after Dennis Burkitt described Burkitt lymphoma (BL) in the same country. BL, of course, is famously associated with Epstein–Barr virus (EBV). Once the viral association between EBV and BL was established, the idea of tumor-causing viruses gained acceptance. It was reinforced by the discovery of the human papillomavirus (HPV)—cervical cancer association. Since then, the possibility of an infectious etiology for human cancers has been on physicians' and epidemiologists' minds. The emergence of HIV-associated cancers suggested an infectious agent as the cause of KS. It led to the

discovery by Chang and Moore of KSHV[8] in 1994. Once the viral etiology of KS was revealed, research began in earnest, and our understanding of the pathobiology of this cancer grew exponentially. To date, PubMed records 17 108 entries under the keyword "Kaposi sarcoma."

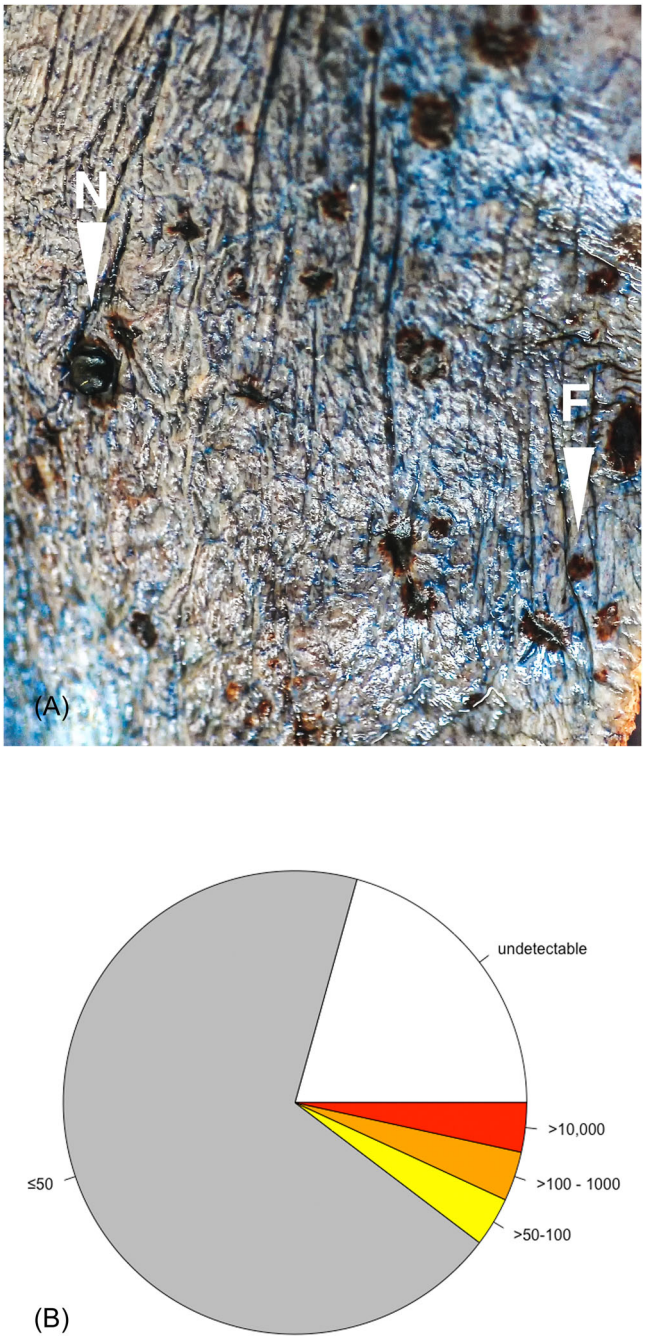

FIGURE 1 (A) Picture of KS lesions in the lung. Arrows indicate a nodular lesion (N) and a flat lesion (F). (B) Distribution of KSHV plasma viral loads (DNA genome copies/mL) in a cohort of 29 PLWH on successful cART presenting with KS requiring cancer therapy (data from[2]). cART, combination antiretroviral therapy; KS, Kaposi sarcoma; KSHV, KS-associated herpesvirus; PLWH, people living with HIV.

2 | KS HAS DIVERSE MANIFESTATIONS BUT A UNIFIED ETIOLOGY: KSHV

A recent estimate counts non-Hodgkin lymphoma, KS, HPV-associated anal cancer, and lung cancer as the most significant cancer contributors to years of life lost among PLWH in the United States; these diseases are concentrated mainly in black PLWH, men who have sex with men (MSM), and the 40–59 year age bracket.[9] The risk of developing KS in PLWH is elevated several 100-fold compared with the general population.[10] The human oncogenic herpesvirus KSHV is the underlying etiological agent for the clinical manifestations recorded at the turn of the 19th century Vienna, in AIDS patients in 1981 New York and San Francisco, children in Eastern Africa, and adults in Xinjiang province in China, today.[11,12]

In KSHV-endemic areas, KSHV acquisition precedes symptomatic disease by many years (the exception being pediatric KS). In 1980s AIDS patients, KSHV seroconversion preceded KS disease by ~33 months.[13] This may be an anomaly, however, brought about by the simultaneous introduction of both HIV and KSHV into a population that experienced high transmission rates for both viruses. It is important to reemphasize that even in PLWH, KS can develop in persons without detectable HIV and near-normal CD4 counts.[3,4] We do not have a specific name for this subtype of KS but would suggest that it not be called AIDS-KS because the patients do not have AIDS, only KS. For this review, we refer to it as HIV-KS.

The unifying principle of all KS is exposure to KSHV. KSHV infection is either accompanied or followed by transient immune deficiency that predisposes a person to KS. If there is no virus encounter, then there is no cancer predisposition. Thus, KSHV partially fulfills Koch's first postulate. Not every KSHV-infected person develops KS, however. Instead, a fixed probability exists that a person infected with KSHV will develop clinically apparent disease. This holds for all the human oncogenic viruses, KSHV, EBV, HPV, human T-lymphotropic virus (HTLV-1), hepatitis C virus, and Merkel cell polyomavirus (MCPyV). The immune status and other factors influence the probability of conversion from infection to clinical disease.

KSHV is present at varying copy numbers in the blood of people who develop KS. For example, Figure 1B shows viral load data from a cohort of PLWH on stable combination antiretroviral therapy (cART) requiring anticancer therapy for their KS.[2] While most patients with clinically apparent disease had detectable KSHV genomes in blood, KSHV viremia with >1000 copies per mL was rare, even for patients with multiple KS lesions. This is consistent with transcriptional profiling data that show most KS lesions harbor latent viruses.[14,15] However, there are exceptions. Some KS lesions transcribe almost the full complement of the viral transcriptome, and the KSHV-associated conditions plasmablastic variant of multicentric Castleman's disease (MCD)[16] and KSHV-associated inflammatory cytokine syndrome (KICS)[17,18] are associated with pronounced systemic viremia.[18,19] KICS patients can have as many as five million KSHV genome copies per mL.[20] KSHV viral load measurements in the blood

TABLE 1 Multiple manifestations of Kaposi sarcoma.

Form	Age in years	HIV	Location
Classic	≥60	–	Italy, Turkey, Saudi Arabia
Endemic	0–16, ≥60	–	Africa, Xinjiang (China)
Iatrogenic	≥60	–	Global
AIDS (epidemic)	16–60	+	US, Europe, Africa
Pediatric-HIV	0–16	+	Africa
Endemic-HIV	0–60	+	Africa
KS-IRIS	0–60	+	Global
Long-term cART	≥60	+	Global
Iatrogenic-HIV	≥60	+	Global
KICS	0–16	+	Global

Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency; KS, Kaposi sarcoma; KS-IRIS, Kaposi sarcoma immune reconstitution syndrome.

may be utilized to detect MCD and KICS, which can cooccur in KS patients.[17,21] While associated with concurrent primary effusion lymphoma (PEL), MCD, and KICS, systemic KSHV viral loads may also correlate with the number of KS lesions or other indicators of disease severity.

KSHV is shed with high frequency in the saliva of infected individuals, particularly while immune suppressed.[22] Saliva is considered the most common route of transmission. Typically, the KSHV genome copy number in the saliva is considerably lower than that of EBV or human cytomegalovirus (HCMV), which also are transmitted by the oral route. This may explain the more limited transmission of KSHV in the general adult population compared to populations where saliva contact is more extensive, such as mother-to-child transmission and transmission among MSM.[23–25]

The multiple types of KS are summarized in Table 1.

(i) Classic KS is a disease of older men around the Mediterranean basin and Saudi Arabia. Classic KS is independent of HIV infection and is concentrated in regions with a population prevalence of KSHV of 4%–9%.[26,27] Disease emergence of classic KS is age-related, perhaps a sign of immune senescence, although no immune biomarker has been identified that correlates with classic KS or can predict it. KSHV serology is not currently used as a screening tool for KS risk. Recent reports document cases of KS in younger HIV-negative gay men, often localized to the foot,[28–30] which would be consistent with the high KSHV transmission rate in this population. One could speculate that pre-exposure prophylaxis for HIV (Prep) without physical barriers does not protect against KSHV transmission.

(ii) Endemic KS is seen among the Kazakh and Uyghur ethnicities in Xinjiang (China) and in Eastern Africa (Kenia, Uganda, Malawi, Zambia, South Africa, and Tanzania). Pockets of high KSHV seroprevalence have also been reported in Amerindians.[31–33] In Eastern Africa, KS is the most common cancer in adult men and is also observed in children. Among the Uyghur, KSHV has also been associated with osteosarcoma, in addition to KS.[34] In endemic regions, the KSHV seroprevalence exceeds 50%, and seroconversion takes place before puberty, that is, mother-to-child or intra-family transmission is the predominant route of infection. Endemic KS is seen in both HIV-positive and HIV-negative persons, old and young, men as well as women. Preliminary studies suggest that KSHV acquisition, if not KS disease, is associated with parasite coinfections in the region.[35,36]

(iii) Iatrogenic KS is seen in solid organ transplant patients (HIV+ and HIV−), and KSHV may be transmitted by the transplanted organ itself.[37] As expected, the prevalence of transplant KS tracks with both KSHV population seroprevalence and the number of kidney transplants in each country, with Italy and Saudi Arabia reporting the highest number of transplant KS cases.

(iv) AIDS-KS or epidemic KS was recognized as an AIDS-defining condition, next to Pneumocystis pneumonia, cryptococcus disease, and histoplasmosis.[1] It is closely linked to HIV infection because of a shared pattern of transmission among high-risk individuals and because of HIV-induced immune deficiency. The HIV pandemic overlaps with different pre-existing classes of KS. Before the introduction of effective Prevention-of-Mother-to-Child-Transmission programs for HIV, pediatric HIV-KS rates were dramatically higher in KSHV endemic regions.[38] Adult HIV-KS rates remain elevated in KSHV endemic regions since most PLWH worldwide reside in areas where KSHV was endemic before the introduction of HIV. In fact, treatment of HIV with cART sometimes leads to a flare-up of KS, a phenomenon termed Kaposi sarcoma immune reconstitution syndrome, which can be alleviated by concomitant oral etoposide.[39]

Lastly, there are familial cases of KS. Here a person or family with inborn immune deficiency becomes exposed to KSHV and develops KS. KS has been reported in a person with Wescott–Aldrich syndrome as well as in persons carrying mutations in the STIM1, the gene encoding stromal interaction molecule 1, OX40, the costimulatory receptor expressed on activated T cells. MAGT1, STAT4, WAS, IFNGR1, and TNFRSF4 have been associated with KS as well.[40–47] These are examples of genes where a single mutation can dramatically increase susceptibility to KSHV acquisition, KSHV reactivation, or KS disease. One would expect many more, less penetrant alleles to segregate in the population (reviewed in[48]).

All types of KS are treated primarily with cytotoxic chemotherapy, mainly using a regimen developed for terminal AIDS-KS before cART was invented.[49,50] In low- and middle-income countries (LMIC) where pegylated liposomal doxorubicin is not affordable in the public sector, free doxorubicin drug, vincristine, or paclitaxel are used.[51] Newer experimental approaches are discussed below. Ganciclovir is active against replicating virus but there currently is no cure for KSHV latent infection and no vaccine against KSHV.

The most significant barrier to understanding KS and developing targeted KS therapies is the absence of small animal models for this tumor or even representative cell culture models. To this day, no one has successfully adapted KS tumor-derived cells to permanent growth in culture. This was not for lack of trying.[52–54] KS-derived explant cultures

and KSHV-infected primary endothelial cells lose the viral genome in cell culture unless the viral episome is under strong selection, such as provided by a selectable marker or the particular genetic makeup of PEL.[55–59] PEL, unlike KS, has numerous genetic abnormalities, some of which, such as mutations in p53,[60] were selected in response to chemotherapy, while others precede therapy. Most PEL also carries EBV.[61] One could speculate that the PEL somatic mutations evolved in the presence of the latent KSHV genome, thus influencing KSHV maintenance, which is required for PEL survival.

From a clinical point of view, the disease manifestation of KS has not changed much since its initial discovery, and the treatment options have not advanced since the introduction of pegylated liposomal doxorubicin. One could argue, therefore, that KS is the same disease as it always was, only the circumstances under which the disease manifests have changed. AIDS-KS has become rarer in the United States and Europe as cART has become readily available, and cancer diagnosis and therapy are accessible to most of the population. KSHV is firmly entrenched in vulnerable populations independent of HIV, and KS is now seen at a younger age. In Sub-Saharan Africa, where most PLWH and most people living with KSHV reside, KS remains prevalent in the general population, and optimal therapy in the form of pegylated liposomal doxorubicin remain unavailable to most patients.

3 | HISTOPATHOLOGY OF KS

KS is a tumor of dedifferentiated or transdifferentiated endothelial cells. This lineage description tries to coalesce several competing interpretations of the mature KS tumor cell's nature and lineage of origin. The diagnosis of KS is based on the WHO definition of KS. The WHO pathology standard defines KS as "*a locally aggressive endothelial proliferation that usually presents with cutaneous lesions in the form of multiple patches, plaques, or nodules, but it may also involve mucosal sites, lymph nodes, and visceral organs. KS is uniformly associated with HHV8 infection, and it represents an example of virus-induced vascular proliferation.*" The WHO uses the presence of KSHV as the sole defining diagnostic criterium for KS.

Positivity for the KSHV genome or a KSHV protein encoded by the virus distinguishes KS from histologically similar, KSHV-negative lesions, such as angiosarcomas.[62,63] The detection of KSHV DNA in KS lesions proved the association between this virus and this tumor beyond a reasonable doubt.[64] It provided the basis for a new approach to KS diagnosis in LMIC.[65] The standard for establishing the presence of KSHV in a tumor lesion is immune histochemistry for the KSHV open-reading frame 73 protein, the so-called latency-associated nuclear antigen (LANA, LNA, or LANA-1).[66–68] No other marker protein has been accepted for the clinical diagnosis of KS. No KS lesion has been described that would carry the viral genome but not express LANA. The LANA promoter is constitutively active in all cell types tested, and LANA is the only mRNA observed in every KSHV-infected cell.[69,70]

Below we expand on two aspects of the WHO definition: the complexity of KSHV transcription in KS and the putative cell types associated with KSHV lesions. The genomic locus for LANA/ORF73 encompasses a series of genes: LANA, vCyc/ORF72, and vFLIP/ORF71. A single leftward transcript originating upstream of the LANA ORF covers the entire region. The vCyc protein is expressed by alternative splicing and from an internal promoter.[71] The vFlip protein is expressed by an internal ribosome entry site on the vCyc-vFlip message.[72] A common proximal 3'-poly adenylation site is used for the transcripts encoding these three proteins; however, a population of transcripts extends further and terminates after the Kaposin/K12 gene. The Kaposin transcript represents the most common mRNA in KS tumors. The large intron of major latency transcript encodes the KSHV micro RNAs (miRNAs),[73–75] except miR-K10a, encoded within the Kaposin ORF.[76] The LANA transcript has been observed by in situ hybridization in KS tumors[77] and KSHV miRNAs have been found in KS tumors and PEL.[78]

There exists considerable heterogeneity of viral transcription across and within KS lesions.[15,79–83] Every KS tumor transcribes the KSHV latency locus, and every KS tumor cell within a clinical lesion expresses the LANA protein. This correlation has biological plausibility since LANA is necessary and sufficient to maintain the KSHV plasmid within the nucleus of any infected cell.[55,84–86] Consistent with this ubiquitous expression pattern, the latency locus is free of repressive chromatin at all times.[87–90] On top of this minimal transcriptional state, which we term "*tight latency*" or latency I analogous to EBV, there exists a gradient of transcription patterns.

These tight latency genes have been demonstrated in individual cells, in all KSHV-associated diseases, and all individual KS lesions. Additional genes are often transcribed in KS and KSHV-associated diseases as well. The data here are less complete and often limited by a lack of reagents. The antibody reagents to the LANA repeat region are more specific and sensitive than any other antibody against KSHV; however, the absence of evidence should not be taken as evidence of absence. In PEL, the LANA-2/vIRF3 locus is consistently transcribed; the LANA-2/vIRF-3 protein is expressed—perhaps also vIRF1 and other genes in this locus. The region around the two lytic origins of replication also seems transcribed under an expanded set of conditions. This includes the viral IL-6 protein, which is typically for MCD.[91,92] Recent single-cell and tumor profiling data suggest the existence of additional actively transcribed regions on the genome in KS and PEL,[14,15,70] a semistable state that we describe as "*extended latency*" or latency II. These include, for instance, the nut-1 nuclear transcript.[77] In addition, the K15 transcript is detectable in PEL, and the K15 protein has been detected in many KS lesions.[93] K15 is located on the right-hand side of the genome. It is variable and differentially spliced, making the RNA difficult to detect.[94,95]

Lastly, about one-third of KS lesions harbor transcripts across the entire viral genome.[14] We call this state "*lytic*." These three prototypical patterns are observed in any set of KS biopsies and any collection of KSHV-infected cells with some variations. The clinical significance of these different transcription patterns is unknown. Still, differential viral transcription and the different cellular compositions of individual KS lesions may explain the clinical observation that not all skin KS lesions in patients on systemic therapy and cART respond equally.

Another feature of KSHV is worth mentioning in this context. All KSHV miRNAs have been observed in circulating extracellular vesicles (EVs) or exosomes isolated from tissue culture supernatant, from KS patients, in the context of viral infection, and from cells that ectopically expressed only the KSHV miRNAs.[96] Detecting the viral miRNAs in EVs or the linear, encapsulated viral genome in plasma thus constitutes a biomarker for KSHV infection. Because EV-encased miRNAs can travel independently of the virus and are not restricted by virus-specific entry receptors, they can induce "KS-like" phenotypes in uninfected endothelial cells.[97,98] This series of experiments independently confirmed that much of the lineage reprogramming induced by KSHV can be attributed to the KSHV miRNAs, most likely in conjunction with paracrine host factors, such as Platelet-derived growth factor (PDGF).[98,99] This phenotype thus increases the heterogeneity of the KS lesion even further. Every KS lesion is an unstable mixture of cells infected with KSHV, not infected with KSHV but reprogramed by EV-transduced KSHV miRNAs, or neither infected with the virus nor carrying the viral miRNAs but exposed to soluble paracrine factors, notably vIL6, IL6, vascular endothelial cell growth factor (VEGF), and PDGF. KS heterogeneity is indistinguishable by morphology.[63,100–102]

Pathologists distinguish patch, plaque, and nodular lesions chiefly based on the degree of spindle cell nests in a section and neoangiogenesis.[103,104] Confusingly, the same terms are also general dermatology terms and have been used to describe the gross appearance of KS skin lesions. In other contexts, the terms flat, raised, and nodular are used to describe KS skin lesions.[105] In response to systemic cytotoxic chemotherapy lesions tend to flatten before they disappear. As noted above, not all skin lesions on a patient respond equally to standard therapy, and not all patients respond. This inconsistent behavior may be due to the cellular and molecular heterogeneity among KS lesions in the same patient. In KS complete responses are rare; partial responses and stable disease represent the most commonly observed outcome, particularly in KSHV-endemic regions.[51,106,107] At times these response classifications are subject to observer bias. Detailed studies of how the overt clinical appearance corresponds to histopathology are missing. The molecular and clinical heterogeneity of KS lesions has foiled clinical trials for multiple targeted agents. Multiple agents such as the VEGF-1 inhibitor Bevacizumab, the mTOR inhibitor sirolimus/rapamycin,[108,109] and receptor-tyrosine kinase inhibitors, such as Imatinib and sorafenib[110–112] show significant efficacy as single agents in small trials for some patients. Still, it is unclear why the other KS patients do not respond. Our lack of a precise understanding of the molecular, histopathological, immune components, and clinical heterogeneity of KS severely hampers the development of rational and targeted therapies.

4 | THE LINEAGE OF THE KS TUMOR CELL

Although the WHO has classified KS as an "*endothelial proliferation*," it has not endorsed any particular histochemical lineage markers for KS diagnosis. Sarcoma biomarkers and endothelial and mesenchymal lineage markers have all been observed in KS lesions. This led to considerable confusion in the field but has not yielded clinically actionable insights.[10] Experimental studies with the KSHV virus in culture added to this mélange of observations. It is essential to keep these two lines of evidence, observations in clinical lesions and experimental infections, separate.

Hong et al.[113] and Wang et al.[114] reported the first host transcriptional profile of KS lesions. These studies and others [102] support the notion that KS is a tumor of endothelial cell lineage, but not just composed of canonical endothelial cells. This sentiment is confirmed by immune histochemistry. KS lesions stain positive for lymphatic endothelial cell lineage markers, such as lymphatic vessel endothelial receptor 1 (Lyve-1), VEGFR3, and Podoplanin, van Willebrand factor, CD31/PECAM-1, CD34. Prox1 and VEGFR3 are perhaps the most specific markers, as they are typically expressed only on lymphatic and not blood endothelial cells.[115] In KS lesions, LANA-positive cells express VEGFR3 (as do some LANA-negative cells).[116] Because KS is highly vascularized, and most lesions undergo active angiogenesis and vessel remodeling, it is difficult to decide for each cell whether it originated from the nest of KS tumor cells (and perhaps lost the virus as it differentiated) or migrated into the lesions as a CD34+/CD31+ circulating endothelial cell precursor cells and then became KSHV-infected and reprogrammed within the KS microenvironment.[117] In KS, unlike any other tumor, there is no distinction between the tumor neovasculature and the tumor itself.

Differentiated endothelial cell markers are not the only ones expressed in KS lesions. Gill and colleagues[118] noted that the Notch isotype expression in KS does not match "normal," that is, fully differentiated endothelial cells. In culture, KSHV can induce Notch and endothelial-to-mesenchymal transition.[119,120] This observation prompted research into inhibiting IC-Notch signaling in KSHV diseases. Unfortunately, the most clinically developed candidate had an unacceptable safety profile. Other markers, such as PDGFRA, have been described in KS or KSHV-infected cells typically associated with mesenchymal lineage or mesenchymal stem cells.[99,121,122] This is expected as "nests" of KSHV-infected tumor cells are embedded in a matrix of stromal cells. Depending on the stage of the particular lesion—patch, plaque, nodular-stromal cells, or even immune cells may make up most of the lesion.

Infection of purified cell populations with KSHV in culture has generated evidence supporting multiple scenarios. KSHV can infect and persist in multiple cell types, perhaps more efficiently in stem cells but also in HEK293 epithelial cancer cells.[117,123,124] In pure culture, infection with KSHV can differentiate precursor cells into lymphatic endothelial cells and transdifferentiate blood endothelial cells (HUVEC) into lymphatic endothelial cells and vice versa.[113,114,125] The endothelial lineage markers PROX1 and SOX18 have roles in the KSHV life cycle.[126] It was also reported that KSHV could differentiate primitive mesenchymal cells into endothelial cells.[127] These culture experiments reinforce the "chicken and egg" problem regarding the trans-differentiation of precursors into more differentiated cells or vice versa. Does KSHV infect mesenchymal stem cells and induce the extraordinary expression of

some endothelial markers, or does KSHV infect mature endothelial cells and dedifferentiate them into more primitive precursors, common ancestors of the mesenchymal/endothelial cell lineage? The in-culture infection experiments suggest that both directions are possible, and that the virus is apt at generating the perfect cellular environment for persistence.

Individual KSHV viral genes, such as K1, vIL6, and vGPCR, in isolation, can dedifferentiate, transdifferentiate and, in rodent systems, fully transform mature endothelial cells.[128–130] The KSHV miRNAs in isolation also induce trans-differentiation and hallmarks of transformation.[76,78,97,98,131,132] In culture, KSHV can transform both endothelial and mesenchymal lineage precursors, as well as experimental cell models, to the point that they form tumors as xenografts in immune-deficient mice.[102,124,133–136] These experiments support the classification of KSHV as a *bona fide* human tumor virus; however, tissue culture systems, by design, are finely tuned to respond to pro-growth signals with drastic changes in cell phenotypes. Some, such as NIH3T3 cells, were evolved to score a single hit (mtP53) or dual hit (Myc and ^{mt}Ras) oncogenes. In culture, both overexpression and mutational activation of single proteins induce transformation. This has been demonstrated for Myc, Ras/h-Ras, GPCR/vGPCR, huIL6/vIL6, and members of the PI3k/mTOR pathway.[137] Myc is the prime example as either amplification, translocation, stabilization, or mutation induces similar phenotypes in susceptible experimental systems and is found in tumors.[58,138,139] The question is not which pathway is more important but which constellation of pathways is active in a particular KS lesion and how it can be targeted therapeutically.

5 | KSHV VIRAL LOAD AS A DIAGNOSTIC MARKER

Oncogenic viruses cause about one-fifth of all cancers worldwide. These viruses are present in all tumor cells, and viral genes (proteins and miRNAs) drive the hallmarks of cancer.[140] One would think, therefore, that viral load measurements constitute a biomarker for viral cancers. This is indeed the case for HPV-associated cervical cancer, where the persistence of viral DNA copies of the high-risk types has become the primary screening tool for preventing the disease. Detecting high-risk HPV is a clinically proven predictive biomarker for cervical cancer and a prognostic marker in HPV-positive oropharyngeal cancer.[141] Likewise, viral load is an established measure for most acute viral diseases. In HIV-infected patients, viral genome copy number is the sole determinant of clinical intervention, that is, cART initiation. Increases in circulating HCMV are the clinically actionable measure to start and stop antiviral therapy in transplant patients. In HCMV, viral load is measured either by genome copy number measured by QPCR or leukocyte antigenemia measured by pp65 levels.[142] Viral load is routinely measured in nasal swabs for respiratory viruses. The COVID-19 pandemic has broadly demonstrated the utility of virus detection in directing public health interventions and initiating antiviral therapy. In sum, a solid body of precedence supports the utility of viral loads as predictive and prognostic biomarkers in any viral disease.

The situation regarding KS is more complicated (reviewed in[6]). Every KS tumor cell carries one or more copies of the KSHV genome and expresses some viral proteins and all viral miRNAs. The presence of KSHV DNA in KS biopsies is under consideration for a rapid field test in KS endemic areas.[65] Likewise, detecting the EBV EBER small noncoding RNAs constitutes the gold standard for diagnosing EBV lymphoma.[143] Yet, herpesvirus loads in plasma or saliva do not have broadly prognostic or predictive power. The problem with using KSHV viral load measurements in blood as biomarkers for cancer is that even cancer-free people have circulating virus in their blood and saliva. Genome positivity for any herpesvirus in blood or saliva is a measure of infection, not an imminent disease as most herpesviruses are shed asymptomatically for life.

There have been many attempts to demonstrate a correlation between KSHV systemic copy number and KS.[144] Reviewing these efforts highlight both difficulties and opportunities. There are three sources of viral DNA in circulation: (i) inside healthy, circulating latently infected cells, (ii) inside infectious virions and noninfectious, sometimes called interfering, particles, and (iii) as part of naked circulating tumor DNA released by the lysis of tumor cells or reactivating latently infected normal cells. These need to be distinguished when testing for clinical associations.

Healthy-latently infected cells characterize the KSHV latent reservoir in normal individuals.[145] We have studied the utility of the KSHV miRNAs as a marker for latent infection and tumor load.[96] Unlike viral DNA, the KSHV miRNA levels do not change markedly during viral reactivation, except for miRNA K12-11. The viral miRNAs are constantly transcribed and processed from the KSHV latency transcript. The mature, correctly processed viral miRNAs are excreted into circulation. Therefore, the viral miRNAs are protected from RNAses. KSHV miRNA levels in blood correlated with tumor burden and the number of healthy, latently infected cells. As of yet, neither approach has entered clinical practice. Developing KSHV viral load measurements in blood represent a diagnostic opportunity for rapid testing and monitoring of therapy response that has not been realized.

6 | VIRUS–IMMUNE INTERACTIONS

Innate immunity is the first line of defense against invading pathogens. Pathogen-associated molecular patterns (PAMPs) on incoming microbes are detected by pathogen recognition receptors (PRRs). Activation of PRRs triggers signal transduction pathways, resulting in the production of interferon and inflammatory cytokines.[146] The KSHV genome encodes many immunomodulatory proteins that prevent antiviral responses from PRRs.[147,148] This immunomodulation allows viral persistence in the host[149] and is reviewed here.

First, toll-like receptors are PRRs that detect incoming microbes in endosomes (TLR3/7/8/9) or on the plasma membrane

(TLR1/2/4/5/6/10).[150] Infection with KSHV activates TLR3,[151] but TLR3-mediated interferon induction is diminished by KSHV viral interferon regulatory factors.[152] The KSHV lytic switch protein, RTA, promotes the degradation of the TLR3 adapter protein, TRIF,[153] and also suppresses gene expression of Myeloid differentiation primary response 88 (MyD88), TLR4 adapter protein.[154]

Second, the nucleotide-binding oligomerization domain-like receptors (NOD-like receptors, or NLRs) are present in the cytoplasm and can also recognize PAMPs. Some NLRs are components of inflammasomes, which upon activation, induce the production of inflammatory cytokines such as IL-1 or IL-18.[150] While the early lytic protein, KSHV ORF45, activates the NLRP1 inflammasome, the tegument protein, KSHV ORF63, can inhibit NLR proteins.[155,156] Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) have traditionally been considered RNA sensors but can also detect DNA viruses like KSHV.[150,157–160] RIG-I is suppressed by the KSHV deubiquitinase ORF64, which prevents RIG-I ubiquitination and activation.[161]

Third, KSHV inhibits cytosolic DNA sensing pathways, including the cGAS-STING pathway. STING on the ER membrane is bound and activated by the cyclic GMP-AMP (cGAMP) generated by activated cGAS. KSHV ORF52 binds to cGAS and prevents the synthesis of cGAMP.[162] Additionally, LANA binds cGAS, preventing TBK1 from being activated,[163] and vIRF1 binds to STING and prevents TBK1 recruitment.[164] In lay terms, an intricate battle ensues with each infection event between the virus and the cell's innate host response. KS is an outcome where the virus wins this battle. We do not know if that represents the majority or a small minority of infection events. We do not know which other factors are involved, but some interchanges are governed by inborn defects and polymorphisms in the human population.[41,42,45]

KSHV modulates cell-mediated immunity. Natural killer (NK) cells, T cells, dendritic cells, and macrophages scour the host for pathogens. Many of these immune cells are capable of identifying and killing virus-infected cells. However, KSHV encodes countermeasures. Many KSHV proteins inhibit NK- or T-cell-mediated killing. For example, the viral ubiquitin ligase KSHV K3 promotes the degradation of MHC-I, CD1d, CD31, and IFN-R1, which prevents CD8+ T lymphocytes from becoming activated and recognizing infected cells. Another viral ubiquitin ligase, KSHV K5, also induces degradation of MHC-I, CD54, B7-2, CD1d, MICA, and MICB, thereby impairing CD8+ T cell and NK cell activity.[165] In addition, MICB expression is downregulated by the KSHV microRNA miR-K12-7.[166] KSHV also subverts CD4+ T cell-mediated immunity. KSHV RTA upregulates an MHC-II antagonist, that is, membrane-associated RING-CH (MARCH8), while promoting the proteasomal degradation of MHC-II.[167] Autophagy is necessary for MHC-II antigen display, but viral B-cell leukemia/lymphoma 2 (vBcl2) prevents it.[168] In addition, IFN and class II MHC transactivator (CIITA) is downregulated by vIRF3, which reduces MHC-II presentation.[169] KSHV LANA binds to the CIITA promoter and prevents IRF4 from activating it, which reduces MHC-II expression.[170]

The cell-extrinsic effects of KSHV on the immune system are, in part, mediated by secreted viral proteins. KSHV encodes three cellular chemokine viral homologs, vCCL1 to 3 (also known as vMIP-I to III).[149] vCCL3 preferentially stimulates chemotaxis in Th2 cells compared to Th1 cells, indicating that viral chemokines may contribute to developing the KS microenvironment's distinctively Th2-skewed milieu.[171] vCCL2 binds to CX3C chemokine receptor 1 (CX3CR1) and CCR5, suppressing the natural ligands of these receptors and preventing the migration of NK cells.[172] vCCL2 also induces CCR3 and CCR8 expression to attract Th2 cells to KS lesions, while inhibiting CCR1 and CCR5 activation.[171] In addition, KSHV encodes an IL-6 viral homolog (vIL-6). vIL-6 signals through gp130 dimers, whereas IL-6 requires IL-6R and gp130 for signaling.[173] Both cytokines activate Janus kinase (JAK)-STAT signaling, primarily through STAT3, which is linked to angiogenesis, migration, differentiation, and cell proliferation.[174,175] The vIL-6 promotes increased IL-6 release, which increases B cell proliferation and causes flare-ups of MCD or KS/PEL.[176] The survival and proliferation of PEL cells are aided by low levels of latent vIL-6 expression.[177] It has been demonstrated that vIL-6 increases the enzyme activation-induced cytidine deaminase production in activated B cells, which increases the rate of class-switch recombination.[178]

7 | IMMUNE TARGETING THERAPIES FOR KS AND KSHV-ASSOCIATED DISEASES

Some label the 21st century as the century when cancer research learned how to appropriate the immune system for cancer therapy. KS and KSHV-associated cancers represent perfect targets, as the viral proteins are considered non-self, and KS and KSHV heavily depend on the tumor and immune microenvironment. After all, transplant KS resolves in response to a reduction in immune suppressive dose and a significant fraction of limited KS resolves after HIV-associated immune deficiency is overcome by cART (eventually, the KS returns in both scenarios).

Anti-IL-6 antibodies were first tested as a therapy for idiopathic MCD, which is known to express significant amounts of human IL-6. Siltuximab, an anti-IL-6 antibody, was effective against KSHV-associated MCD.[179] Tocilizumab, an anti-IL-6R antibody, was tested in a small cohort of KSHV-associated MCD patients and was found to show activity.[180]

Programmed death ligand 1 (PD-L1) is an inhibitory molecule overexpressed on many different tumor types. PD-L1 binds to its receptor, programmed cell death protein 1 (PD1), to suppress immune responses. Increased PD-L1 expression in monocytes induced by KSHV infection may help KSHV evade the immune system.[181] PD1 is persistently increased in NK cells recovered from KS patients, indicating an exhausted phenotype.[182] Nivolumab and pembrolizumab are examples of anti-PD1 antibodies that reduce tumor size in KS patients harboring HIV[183–185] as well as in classic and endemic KS.[186] Pembrolizumab was previously shown to have an acceptable safety profile in HIV patients with cancer.[185]

Further studies are ongoing, as it is unclear how these drugs affect HIV latency.[187,188] These include trials investigating intralesional injections of Nivolumab in cutaneous KS (NCT03316274) and

pembrolizumab in combination with anti-retroviral therapy in HIV-infected individuals with cancer (NCT02595866). Another inhibitory modulator of T cells is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[189] Ipilimumab is an anti-CTLA-4 antibody and, in combination with Nivolumab in KS patients, displayed good efficacy.[190,191]

Pomalidomide and Lenalidomide,[2,192,193] both derivatives of Thalidomide, represent the only new drug class approved for treating KS in the last 20 years. Pomalidomide was safe and active in KS patients with and without HIV, with an overall response rate of 71%.[194] This led to accelerated approval in the United States of America. Several more extensive studies are ongoing worldwide (NCT04577755, NCT02659930, NCT03601806). These will establish the efficacy of pomalidomide across diverse populations of KS patients. Their primary target is Cereblon, which is an essential gene in PEL.[195] In addition to its cell intrinsic role in survival, pomalidomide modulates the immune response at both a cellular and systemic level.[196] Pomalidomide restores B7-2, ICAM-1, and MHC1 levels in latent and lytic PEL cells.[197] In addition, this drug also prevents tumor cells from upregulating PD-L1.[198] It may kill virally infected cells in the KS lesion directly, render them visible to the adaptive immune system, or modulate the inflammatory lesion microenvironment to the point where it can no longer sustain tumor cell proliferation by intrinsic or paracrine modulators.

In sum, we hope that this review has highlighted that most patients that develop KS today are nothing like the AIDS-KS patients that led to the discovery of KSHV and the formulation of chemotherapy-based KS treatments. KS patients today are diverse; they experience KS under different circumstances and exhibit different but still underdefined phenotypes of KSHV infection. We lack a clear understanding of what exactly goes on in the KS lesion microenvironment and which are the rate-limiting molecular processes that maintain this cancer. We have no outcome markers beyond lesion measurements and no predictive or prognostic molecular tests. The KS and HIV-KS epidemic cannot be considered solved; it remains rampant, particularly in LMIC environments where the best standard of chemotherapy care is not widely affordable. We are still learning to optimally target KSHV to treat KS and monitor KSHV to predict KS. Pomalidomide and cART provide a new oral treatment modality for KS.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

As this is a review, the data are available in PubMed and as listed in references. The data that support the findings of this study are openly available in pubmed.

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