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Diagnosis and Treatment of Kaposi Sarcoma

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Abstract

Kaposi Sarcoma (KS) is the most common neoplasm of people living with HIV today. In Sub-Saharan Africa KS is among the most common cancers in men, overall. Not only HIV+ individuals present with KS; any immune compromised person infected with Kaposi Sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 is at risk: the elderly, children in KSHV-endemic areas, and transplant recipients. KS diagnosis is based on detection of the viral protein LANA in the biopsy, but not all cases of KS are the same or will respond to the same therapy. Standard KS therapy has not changed in 20 years, but newer modalities are on the horizon and will be discussed.

1. Introduction

It is somewhat disheartening, but after 20 years of intense research the cell of origin of Kaposi Sarcoma (KS) remains elusive. KS displays broad clinicopathological variation depending on (i) location of KS lesions (lymph node, internal, or cutaneous), (ii) clinical stage (patch, plaque, nodular) and (iii) epidemiological classification. The latter includes classic KS in elder men, African (endemic) KS in younger African men and children from central Africa, iatrogenic KS (mainly in transplant patients, but also due to chemotherapy and other immune suppressive therapy) and epidemic HIV / AIDS-associated KS [1]. Endemic KS includes a nodular clinically indolent form, an aggressive variant with large invasive cutaneous tumors with involvement of underlying soft tissue and bone, and an endemic-pediatric variant that presents as lymphadenopathy in young children [2, 3]. The overwhelming majority of epidemic HIV-associated KS occurs in men who have sex with men, but women, children, intravenous drug addicts and recipients of organ transplants are also affected [4]. Additional clinicopathological sub-groups of epidemic KS comprise HIV-associated KS on combined antiretroviral therapy (cART), HIV-associated KS with no or

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Compliance with Ethical Standards

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failing cART, i.e. end-stage AIDS, HIV-associated pediatric KS, and KS associated with immune reconstitution inflammatory syndrome (IRIS) [5]. Current evidence indicates that pediatric KS, regardless of the epidemiologic variant, is different from adult KS with an increased risk for disseminated and progressive disease [6]. The wide clinicopathological spectrum of KS suggests that KS does not represent a single disease. Yet, they are all treated the same: surgery/cryotherapy for superficial skin lesions and liposomal doxorubicin (Doxil™) as first-line therapy for systemic and more extensive forms of KS [7, 8]. Recently, more treatment options have gained acceptance and newer targeted therapies show promise in clinical trials.

2. Kaposi Sarcoma-associated herpesvirus (KSHV)

All variants of KS are caused by Kaposi sarcoma-associated herpesvirus (KSHV) [9–12] [13]. KSHV comprises six major subtypes (A, B, C, D, E, and F). Genetic variability of ORF-K1 gene sequences correlates to 13 different variants of KSHV [14]. Limited evidence exists that certain KSHV subtypes may correlate with more aggressive disease or with particular epidemiological types of KS [15, 16].

The molecular biology of KSHV has recently been reviewed in detail [17]. For the purpose of this article it is important to recall that KSHV is a double-strand DNA virus, which encodes more than 80 proteins and an extensive set of micro RNAs. The virus is enveloped and uses a virus-encoded DNA-dependent DNA polymerase (orf9) for genome replication during the lytic phase. The viral polymerase is sensitive to the drugs ganciclovir and foscarnet, but not to acyclovir. Like other herpesviruses KSHV also encodes a large number of genes that help it to escapes immune destruction during primary infection. These relate to the inhibition of the interferon response, anti-apoptosis factors, autophagy inhibitors, and also oppose Natural Killer (NK) cell-mediated control of KSHV infection (reviewed in [18]).

KSHV like all herpesviruses establishes molecular latency, including in KS tumor cells. At any given time only a low percentage of KS tumor cells replicate the virus, while the majority of cells only express the viral latent genes and viral latent miRNAs [19–21]. This gene expression pattern suffices to maintain KS lesions. The viral latency associated nuclear antigen (LANA) alone is necessary and sufficient to maintain the viral episome in dividing infected cells [22] (Figure 1); however, there exists evidence that lytic replication is required for systemic persistence, oncogenesis, and disease progression [23]. Obviously, viral replication is required for transmission, independent of KS lesion status.

Transmission of KSHV is chiefly by horizontal transmission through saliva [24–28], though extensive, repeated contact is needed to establish transmission, such as it occurs in mother-to-child or sexual interactions. This scenario represents an important distinction to Epstein-Barr-Virus, which is present at significantly higher levels in saliva and readily transmitted, e.g. in college settings, where it leads to infectious mononucleosis. For adults heterosexual transmission of KSHV is not considered significant, but sexual transmission between MSM is important to explain the elevated population prevalence. KSHV seroconversion correlates with contact number [26]. Here too, saliva is considered to be a major factor. Transmission

of KSHV though blood transfusions is rare, isolated cases of transmission by organ transplant have been reported [29], while vertical routes of transmission appear to be unimportant.

The fact that KS develops in HIV-negative transplant patients as well as in AIDS patients suggests that HIV in itself is not required for KS. The fact that the risk of developing KS is higher in KSHV seropositive HIV+ patients than in HIV− transplant patient, suggests that HIV infection may generate a qualitatively more deleterious immune deficiency than chemical or drug induced T cell inactivation. This notion is supported by results from the START trial [30]. Here, fewer patients developed KS if ART was started immediately at 500 CD4 cells/mm^3 compared to deferred therapy initiation at still respectable 350 CD4 cells/mm^3. Alternatively, HIV viral replication, HIV proteins, or HIV-associated immune activation may result in KSHV reactivation. On the one hand KSHV replication is known to precede KS tumorigenesis and this may explain the prophylactic efficacy of ganciclovir [23, 31], a KSHV polymerase inhibitor. On the other hand, KSHV replication is not required to maintain existing KS lesions, as these contain KSHV mostly in its latent form, which may explain why gancilovir had no effect on established KS lesions [32, 33].

T-cell specific immunosuppression is a well-recognized cofactor in late stage AIDS-KS and in transplant-associated KS, but less so in classic KS, HIV-negative endemic KS and in KS that develops in HIV-positive person on successful therapy, i.e. with near normal CD4 counts and undetectable HIV viral load. Whether persons that develop KS in the absence of massive CD4 cell deficiency suffer from more subtle impairments, such as anergy, immune senescence, loss of T cell repertoire [34], or whether there exist tumor triggers that operate entirely independently of immune surveillance is the subject of ongoing scientific inquiries.

3. Cell Lineage / origin and Differentiation in KS

The spindle-shaped cells in KS lesions are believed to be of endothelial lineage [35, 36], though they also have features of smooth muscles cells and pericytes [37–39]. There is even evidence that KS is a mixture of tumor cells. Even though spindle cells comprise the bulk of the lesion and the proliferating fraction, they may not be the driver population. Other stromal components, such as pericytes or even macrophages may be necessary to sustain the lesion and may secrete essential, lesion-driving paracrine factors [40]. If so, then targeting these cell populations, even though they are in a minority, may lead to advances in KS therapy. Finally, tumor stem cells in KS could perpetuate the tumor and spawn the highly proliferative spindle cells. Endothelial stem cells would be de-differentiated or trans-differentiated lineage specific endothelial cells (lymphatic endothelial cells (LEC) or blood-vessel endothelial cells (BEC)) [35–37, 41] that acquire traits of “stemness” (shared molecular pathways that underpin the fundamental stem cell properties of self-renewal and specific cellular differentiation), such as defined by loss of differentiation markers or gain of stemness markers, e.g. primitive mesenchymal cells.

4. Update on KS epidemiology – Classic, AIDS- and transplant KS

The epidemiology of KS in the US, i.e. an area of low KSHV and HIV seroprevalence and primarily adult transmission in high-risk groups, is driven by AIDS-KS between MSM and classic KS in the elderly. Figure 2 summarizes the most recent data as collected in the SEER database. Since only 6% of cases were female, only male cases are included. Firstly, KS incidence rates are stratified by age group (<65 and 65+) as a crude surrogate to separate classic and HIV-associated KS in a low KSHV seroprevalence region. Secondly, KS incidence rates are stratified by race. The peak of the US KS epidemic between 1981 and 1997 is clearly evident (Figure 2, panel A). Since 1997 the KS incidence has remained level at ~ 1/100,000. Today, we see as many cases developing in younger males as in older males. The incidence of AIDS-KS no longer declines after the year 2000 as both KSHV and HIV are now established in the US population. Dermatologists and oncologists will continue to see and treat KS lesions.

These SEER data indicate a significant race/ethnicity disparity with respect to KS incidence and response to treatment. The HIV epidemic “hit” the black communities in the US somewhat delayed, but has continued at a higher level up to today [42]. This is reflected in a significantly higher rate of KS even in the most recent years (Figure 2, panel B). The 5-year survival for black KS patients is significantly worse than for white KS patients (Figure 2, panel C). All of the KS cases in blacks are in younger men (0–44 years old). In that age bracket the survival disparity continues to this day. In the 1990–1992 calendar period the 5-year survival for whites was 19.2% compared to 15.1% for black KS patients. In the most recent 2006–2012 calendar period the 5-year survival for whites was 75.3% compared to 59.4% for black KS patients. The reason for this discrepancy is unclear, but may point to a need for increased screening and education in addition to better treatment and overall health resources.

5. Update on KS epidemiology – Endemic, AIDS-KS

The epidemiology of KS in Sub-Saharan Africa and South Africa, i.e. an area of high KSHV and substantial HIV seroprevalence is driven by AIDS-KS and endemic KS in the elderly and children. Here, transmission is seen in the pediatric population (mother-to-child) as well as in the adult population and KSHV seroprevalence was substantial prior to the emergence of HIV. High quality incidence data are difficult to obtain, but WHO globocan [43, 44] and several other studies indicate that KS continues to comprise a significant percentage of total cancer burden in Sub-Saharan Africa, with 24% in Mozambique, 27% in Uganda and 35% in Zimbabwe [45–52]. The introduction of ART has significantly reduced the incidence of KS in HIV-infected patients, as eloquently illustrated by Bohlius et al. [53], who found that the early introduction of ART decreased the risk to develop KS by 80% in a cohort of HIV-infected South African patients. KS continues to increase in South African pediatric patients [54]. The HIV epidemic on the African continent is most severe in South Africa and in 2015 approximately 7 million South Africans lived with HIV. Despite the introduction of ART and actions to fight HIV infection, an estimated 380,000 new infections occurred in South Africa and 180,000 patients died from AIDS-related illnesses in 2015 (UNAIDS gap report as cited in http://www.avert.org). In 2015 HIV prevalence in South Africa varied between

regions from 18% to 40% amongst adults, despite the fact that the South African ART program is the largest one in the world (http://www.who.int/hiv/pub/arv/global-aids-update-2016-pub/en/). KS will therefore continue to be a major cancer burden during the next few years.

6. Diagnosis and Pathology

Although KS can be strongly suspected in an appropriate clinical setting, recent studies confirmed the limited predictive value of clinical diagnosis of KS [55]. Histopathological confirmation of a diagnosis of KS remains the gold standard, but the diagnosis is often not straight forward, especially if pathologists are not familiar with the spectrum of histopathological features of KS. Histopathological diagnosis of early stage KS depends on the detection of subtle clues that can be easily missed by the pathologist [56]. Well-established clinical lesions of KS however typically, but not always, display characteristic histopathological features that can be accurately diagnosed by a trained histopathologist [57–60].

The wide morphological spectrum of KS may mimic numerous unrelated non-neoplastic and neoplastic conditions, presenting a diagnostic pitfall to the pathologist. Pathologists should be aware of recognized variants of KS including anaplastic, telangiectatic, lymphangioma-like, cavernous hemangioma–like, pyogenic granuloma–like, intravascular, bullous, ecchymotic, hyperkeratotic, keloidal, micronodular, glomeruloid, solid, keloidal, desmoplastic, KS with myoid nodules, KS with sarcoidlike granulomas and pigmented KS [57–61]. Spindle-shaped cells are present in all forms of KS [62]. They represent a unifying feature, form the basis of diagnosis, and constitute the bulk of the proliferating cell fraction as ascertained by Ki-67 stain or by other molecular markers of proliferation.

In almost all KS biopsies spindle-shaped cells are infected by KSHV [63]. KSHV is necessary for KS development [26, 64]. All KSHV-infected cells transcribe so-called latent messenger RNAs and a minimal set of viral proteins [19, 21, 65]. The KSHV latency-associated nuclear antigen (LANA) has become the deciding diagnostic marker for KS. LANA-specific monoclonal antibodies are robust and are commercially available for automated immunohistochemical staining system. They are directed against a highly antigenic repeat motif in the center of the protein EQEQE. A positive LANA stain unequivocally confirms a diagnosis of KS in the appropriate clinicopathological context [66–69]. However, LANA expression may also be present in other KSHV associated conditions including multicentric Castleman’s disease, primary effusion lymphoma, and lymphoma arising in KSHV-associated multicentric Castleman’s disease [70]. LANA expression is therefore not confined to KS lesions [65, 71, 72]. KSHV DNAemia is commonly present in HIV+ patients with KS at the time of ART induction or with progressive KS, but undetectable in almost all patients on ART and those with regression of KS [19, 73].

LANA staining, however, is variable. It depends to some degree on the clinical progression stage of the disease, particularly in skin lesions. Superficial lesions or lesions that develop in patients on stable combination antiretroviral therapy (cART) may have very few LANA

positive cells [74]. In patients with multiple lesions there can be a tendency to biopsy milder lesions to minimize bleeding and these tend to have fewer spindle cells and among those fewer LANA positive cells. The variable staining pattern for LANA in KS cells does not relate to patient age, gender, clinical subtype of KS, the distribution or extent of KS lesions, or CD4 count [75, 76]. Although stage of KS and the immunohistochemical method have been shown to influence variable staining for LANA in KS cells, the factors that influence the level of LANA expression remain unknown [76].

The absence of detectable LANA expression on immunohistochemistry may be due to technical reasons or very low viral copy numbers within KS cells. Failure to demonstrate LANA does not necessarily rule out KS in an appropriate clinicopathological setting [77]. In such cases, LANA-stained sections should be carefully re-assessed for subtle granular staining in KS cell nuclei [76]. PCR has been shown to reliably detect HHV-8 in KS lesions even in the absence of LANA expression [77, 78]. However, recent studies highlighted potential contamination of KS biopsies with subsequent false positive PCR results for HHV-8 [79]. Negative LANA expression should therefore always prompt very careful reconsideration of all clinicopathological features and potential alternative conditions should be considered in the differential diagnosis.

7. Update on treatment approaches

The FDA-approved treatment modalities for KS have not changed in 20 years. This may seem disappointing at first glance, but it also implies that we have 20 years of experience with the current standard of care. As KS manifests in many forms, therapies should also be divided into multiple application scenarios.

AIDS-KS responds to immune reconstitution and HIV suppression. Depending on geographic location and severity of presentation, 50% of AIDS-KS responds to cART [80–85]. State of the art cART and monitoring of its efficacy are essential in the treatment of AIDS-KS and often suffice. The goal is to reconstitute the immune system and suppress HIV replication, either in the context of treatment naive patients where KS lesions are the first indication of HIV infection, or in the context of AIDS, where KS lesions indicate HIV cART failure. A fraction of AIDS-KS responds to introduction of cART with disease progression. This phenomenon has been termed KS immune reconstitution syndrome (KS-IRIS) [86–88]. It is seen in as many as 10% of patients exposed to cART for the first time, particularly in Africa. The cause of this manifestation of KS is unclear. Clearly withdrawing cART is not an option, but concurrent chemotherapy and perhaps immune modulating adjuvants may be beneficial in the short-term [89]. Importantly though, both KS disease stabilization as well as disease acceleration have been reported in response to steroids [90, 91]. If and how other modulators of inflammation and immunoactivation would work is unknown.

There are several studies that suggest that HIV protease inhibitors, and in particular nelfinavir, have direct anti-KS activity in addition to their anti-retroviral therapy [88, 92–94]. There are also reports that fail to see a clinical benefit in KS comparing non-protease inhibitor containing regimen to protease inhibitor containing regimen [95]. Pre-clinical data on the efficacy of nelfinavir against KS and other solid tumors are encouraging, but it is

difficult to judge how these would translate into clinical practice. Several trials of nelfinavir against KS and other solid cancers are ongoing, but no outcomes are available. In this regard it is noteworthy that many modern cART regimen no longer contain protease inhibitors. For instance, Gilead uses cobicistat in its NNRTI-based medication: elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil. Cobicistat like the protease inhibitor ritonavir boosts drug concentrations by inhibiting P450 metabolism, but has no protease inhibitory activity.

A third of AIDS-KS in the US now develops in the context of successful cART, i.e. in patients with undetectable HIV viral load and near-normal CD4 counts [96, 97]. We know that even these patients experience HIV disease, either in the form of unspecific, systemic immune activation or as a result of incomplete CD4 T cell receptor reconstitution after symptomatic HIV disease [98].

Transplant-KS responds to immune reconstitution, though lowering the immunosuppressive dose risks graft rejection. Here KSHV can be acquired before transplant, after transplant or through the transplant [4, 29, 99, 100]. Switching the chemical immune suppressive regimen from cyclosporine A/FK506 to mammalian target of rapamycin (mTOR) inhibitors such as rapamycin/sirolimus/everolimus often leads to KS regression [101, 102]. The mechanism of action is the subject of investigation. One difference between cyclosporine A and sirolimus is that cyclophillin, the target of cyclosporine is only expressed in T cells, whereas mTOR, the target of rapamycin is expressed in T cells, B cells, endothelial cells, and in most KS tumors. Even established KS lesions respond to rapamycin directly and independently of immune reconstitution in AIDS KS [74] and immunodeficient preclinical models [103], though rapamycin primarily stalls tumor growth leading to stable disease rather than inducing tumor regression outright.

Cytotoxic chemotherapy represents the standard of care for KS [104] including in children [105]. DNA damaging agents, such as doxorubicin are effective in 60–80% of KS in the US, which conversely implies that state of the art therapy fails in up to a third of KS patients (Figure 2). The median survival in response to cytotoxic chemotherapy is worse in resource-limited settings and populations with less than optimal access to HIV and cancer care (Figure 2). Liposomal formulations of doxorubicin or daunorubicine minimize systemic toxicity [106, 107], In addition, paclitaxel also shows clinical efficacy against KS [108–111]. It is often considered as second line therapy or used in situations where doxorubicin is not available.

VEGF is essential for endothelial proliferation and inhibition of VEGF constitutes a rational therapeutic approach for Kaposi Sarcoma. Thus far, however, clinical trials of single agent trials of VEGF neutralizing antibodies or VEGF-receptor inhibitors (bevacizumab, imatinib) have been ambiguous [112–115]. Anti-VEGF therapy worked in some patients, but not others. This variable results may be due to inadequacy of drug delivery to the KS lesion, the overall performance status of the patients, and redundancy in angiogenic factor signaling, as VEGF, bFGF and PDGF all contribute to KS growth [116, 117]. In other solid tumor indications angiogenesis inhibitors such as bevacizumab are used in the adjuvant setting and we speculate that this would have utility in KS as well. Further downstream acting drugs, such as the mTOR inhibitor sirolimus have shown clinical efficacy in transplant KS and it

may be interesting to explore more potent VEGFR/c-kit inhibitors such as cabozantinib, pan-kinase inhibitors such as sorafenib, or anti-VEGF antibodies with different pharmacokinetics or intralesional applications.

IFN-alpha and its pegylated derivatives have been used with some success in the early days of the AIDS epidemic and against classic KS [118–121]. Doxil has now largely replaced IFN-alpha. It is noteworthy, however, in that the clinical success of pegylated IFN-alpha provided the first in human evidence for the extreme immune reactivity of KS. It has since been observed in the context of other immune modulatory drugs [122]. A fraction of KS, like a fraction of melanoma (reviewed in [123]), will spontaneously regress. Many, though not all, transplant KS as well as AIDS-KS lesions will regress upon immune reconstitution alone. The molecular mechanisms of these seemingly spontaneous regression events are unclear, but support further explorations in this area.

Imiquimod is a TLR7 agonist with non-specific activity against a variety of conditions. It is FDA approved as a topical formulation for the treatment of actinic keratosis and superficial basal cell carcinoma. Since 2015 generic forms of imiquimod are available. TLR7/8 agonists reactivate KSHV [124], but imiquimod was one of the weaker stimulants in this experimental system. If this reactivation leads to virus release, this in turn may stimulate tissue and tumor-resident antigen presenting cells [125]. At this point several cases of skin KS responding to topical treatment with imiquimod have been published, as have been treatment failures [126–128]. A systemic clinical trial has not been conducted.

Another group of agents, with promising clinical experiences [129–132] includes thalidomide and it's more active derivatives pomalidomide and lenalidomide. These agents have broad immunomodulatory, anti-angiogenesis properties, targeting NFκB among others and are the subject of ongoing clinical studies. Like other immunomodulatory agents, one could speculate that their benefit will be most pronounced in the setting of limited KS, classic KS, or as adjuvant to chemotherapy.

Immune checkpoint inhibitors have gained notoriety because of their overwhelming efficacy in a select group of immunoreactive cancers, including melanoma and polyomavirus associated Merkel cell carcinoma [133–136]. It is likely that these agents will be also be active against KS, although clinical evidence has not been formally reported. Nivolumab is a humanized monoclonal antibody directed against PD-1, which is a negative co-receptor that is expressed on activated T cells. Ipilimumab is a humanized monoclonal antibody directed against CTL4. Small studies suggest that KS tumor cells do not express the T cell co-stimulatory molecules CD80 and CD86 [137]; the expression of the T cell inhibitory molecule PD-L1 and PD1 is variable and needs to be explored further [138, 139]. At present the AIDS malignancies clinical trials consortium (AMC) is conducting a phase I/II trial of nivolomab alone or in combination with ipilimumab in Kaposi Sarcoma (NCT02408861).

8. Summary and Outlook

In sum, Kaposi Sarcoma will continue to be seen at elevated frequencies in people living with HIV/ AIDS. It remains the most common cancer in regions that were endemic for

KSHV and now experience substantial co-infection with HIV. People co-infected with HIV and KSHV are at risk of developing KS even if HIV is controlled by cART and this risk will increase as a person ages. The histopathological diagnosis of KS is not trivial, but greatly improved by the detection of LANA in biopsies of KS lesions. Detection of KSHV DNA or RNA is not yet developed to the same standard of accuracy. Doxil and Paclitaxel are efficacious against KS, but also associated with significant toxicity. Newer approaches such as sirolimus, VEGF/VEGF receptor inhibitors and immune modulatory agents show promise, but we do not yet know which types of KS and which kind of patients will benefit the most from these new agents. In the early days of the AIDS epidemic, skin KS was extensive and often accompanied by systemic KS, requiring systemic drug delivery. In the era of concurrent cART and complete HIV suppression, many HIV+ KS patients present with only localized lesions and may benefit from intralesional therapy alone or newer agents with more limited toxicity than standard dose chemotherapy.

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Key points

- Kaposi Sarcoma continues to be among the most common causes of morbidity and mortality in people living with HIV worldwide.
- There is evidence for multiple types of Kaposi Sarcoma, dependent on clinical presentation, cofactors and viral gene expression.
- New approaches to Kaposi Sarcoma are under development.

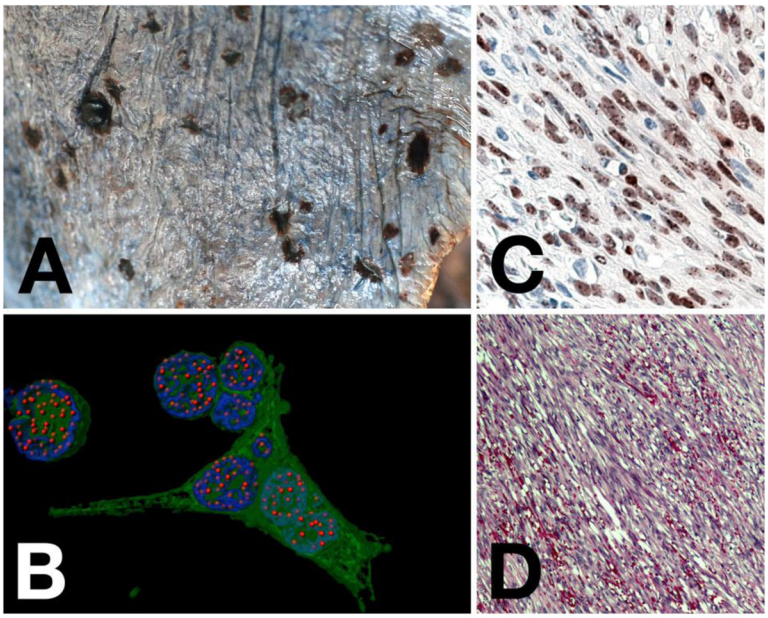

Figure 1. KS pathology and histology

Panel A shows an image of gross morphology of disseminated KS on the surface of the lung. Note the single, raised, nodular lesion in the upper left, as compared to the flat lesions. Panel B shows a computer-enhanced image of immunofluorescence in a KSHV recombinant virus that also expressed green fluorescent protein (gfp) in a PEL cell line. LANA staining is in red, nuclear DNA staining in blue and gfp (to indicate infected cells) in green. This analysis clearly shows the presence of discrete “LANA dots”, each indicating a place where the viral genome is tethered to the host chromosome. Panel C shows an image of LANA staining of a KS lesion by immunohistochemistry (brown) with hematoxilin counterstain (blue). Note all LANA staining is nuclear and the appearance of darker spots or dots within the nuclear staining. Panel D, shows an H&E stain of a KS lesion. Note the spindle shape nature of the cells, which are of endothelial cell lineage. Slit-like spaces in between the cells contain extravasated red blood cells.

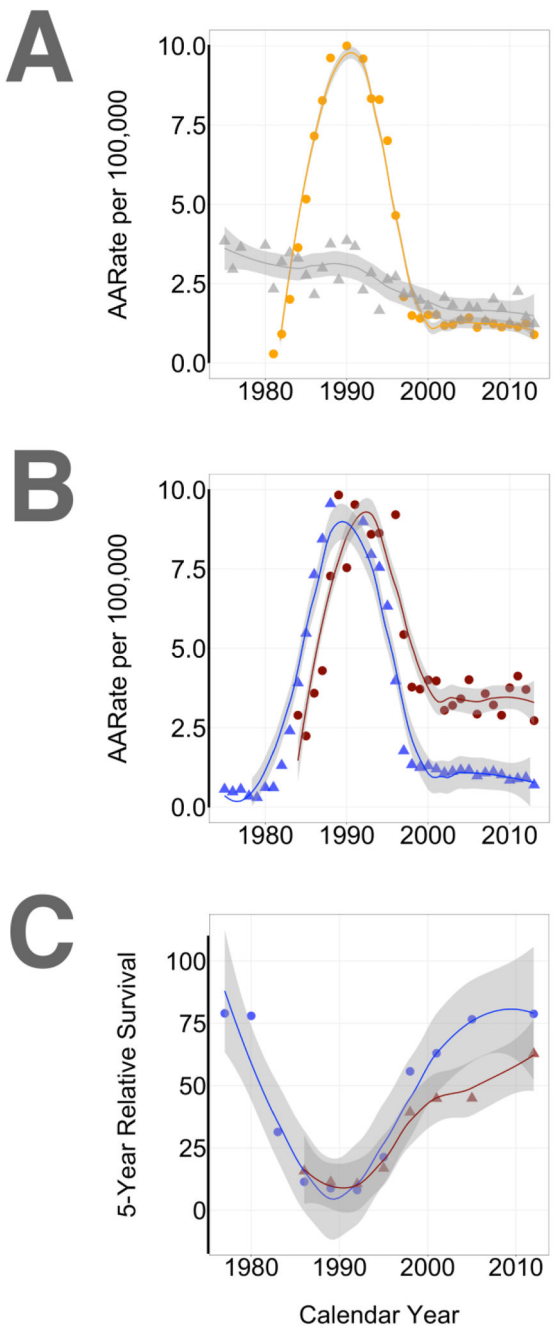

Figure 2. Review of KS incidence rates based on US SEER data (10-15-2016)

Data and graphs were obtained using the SEER data website (http://seer.cancer.gov/explorer/). For panels A–B the calendar year is shown on the horizontal and incidence rate per 100,000 on the vertical axis. Panel A stratifies data by age (orange circle: <65 and gray triangle: >65+). Panel B stratifies data by race/ethnicity (red circle: African American and White: blue triangle). Panel C shows 5-year survival by calendar interval and also stratifies data by race/ethnicity (red circle: African American and White: blue triangle).