Cancer Association of South Africa (CANSA)

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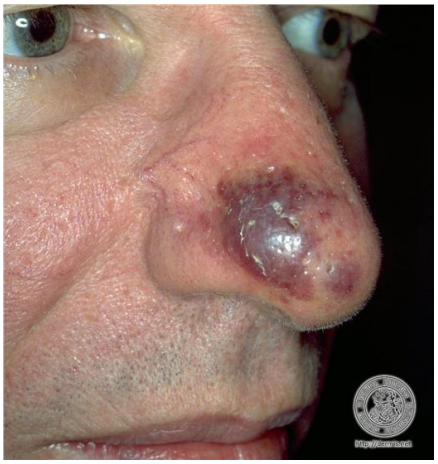
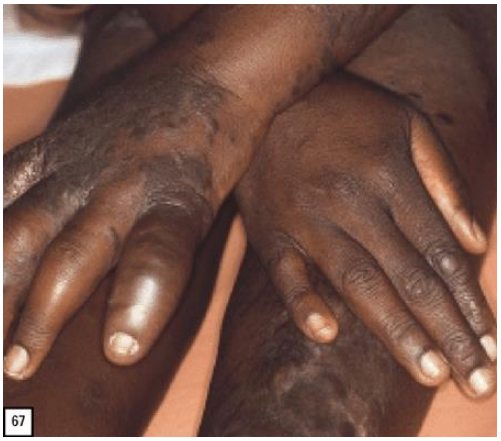
Fact Sheet
on
Kaposi Sarcoma

Introduction

Kaposi Sarcoma (KS) is a cancer that causes patches of abnormal tissue to grow under the skin, in the lining of the mouth, nose, and throat or in other organs. The patches are usually red or purple and are made of cancer cells and blood cells. The red and purple patches often cause no symptoms, though they may be painful. If the cancer spreads to the digestive tract or lungs, bleeding can result. Lung tumours can make breathing difficult.



[Picture Credit: Kaposi Sarcoma]



Before the HIV/AIDS epidemic, KS usually developed slowly. In HIV/AIDS patients, though, the disease moves quickly. Treatment depends on where the lesions are and how bad they are. Treatment for HIV itself can shrink the lesions. However, treating KS does not improve survival from HIV/AIDS itself.

[Picture Credit: Kaposi Sarcoma 2]

Kaposi Sarcoma

Kaposi Sarcoma (KS) is a multicentric, malignant neoplastic vascular proliferation characterised by the development of bluish-red cutaneous (on the skin) nodules, usually on the lower extremities, most often on the toes or feet, and slowly increasing in size and number and spreading to more proximal areas. The tumours have endothelium-lined channels and vascular spaces admixed with variably sized aggregates of spindle-shaped cells, and often remain confined to the skin and subcutaneous tissue, but widespread visceral (body organ) involvement may occur.

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Bishop, B.N. & Lynch, D.T. 2020.

"Kaposi sarcoma is an interesting soft tissue tumor occurring in several distinct populations with a variety of presentations and courses. In its most well-known form, Kaposi sarcoma occurs in patients with immunosuppression, such as those with acquired immunodeficiency syndrome (AIDs) or those undergoing immunosuppression due to an organ transplant. Initially described in 1872 by Moritz Kaposi, an Austro-Hungarian dermatologist in 5 patients with the multifocal disease, human herpesvirus/Kaposi sarcoma herpesvirus (HHV-8) was discovered as a causative agent of Kaposi sarcoma as the AIDS epidemic progressed in the 1980s. Four clinical forms emerged.

1. Classic form occurring in elderly men of Mediterranean and Eastern European descent on the lower extremities
2. Endemic African form with generalized lymph node involvement occurring in children
3. HIV-related form occurring with patients not taking highly active antiretroviral therapy (HAART) with diffuse involvement of the skin and internal organs
4. Iatrogenic form in immunosuppressed patients also with diffuse involvement of the skin and internal organs

Each form has a differing natural history ranging from indolent to more aggressive and fatal in anaplastic varieties."

Incidence of Kaposi Sarcoma in South Africa

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of Kaposi Sarcoma cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	987	1:338	2,47%
Asian males	10	1:1 273	1,03%
Black males	879	1:286	6,72%
Coloured males	48	1:660	0,98%
White males	50	1:642	0,21%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	578	1:660	1,39%
Asian females	6	1:1 875	0,47%
Black females	522	1:561	1,80%
Coloured females	27	1:1 251	0,59%
White females	23	1:1 420	0,13%

The frequency of histologically diagnosed cases of Kaposi Sarcoma in South Africa for 2017 was as follows (National Cancer Registry, 2017:

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	10	121	494	289	113	40	10	10
Asian males	0	2	3	5	0	0	0	0
Black males	9	110	352	261	98	36	6	7
Coloured males	0	7	20	12	6	2	0	1
White males	1	2	19	11	9	2	4	2

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	15	155	226	105	43	20	11	3
Asian females	0	2	3	1	0	0	0	0
Black females	15	133	209	95	39	20	1-	1
Coloured females	0	11	9	4	2	0	1	0
White females	0	9	5	5	2	0	0	2

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Kaposi Sarcoma

Kaposi sarcoma (KS) is a tumour caused by Human Herpes Virus 8 (HHV8), also known as Kaposi's Sarcoma-associated Herpes Virus (KSHV). It differs from other cancers as it starts in several areas of the body at once, while other forms of cancer start in one place and then spread.

Kaposi sarcoma is now far more common and spreads more aggressively through the body among patients with Aids.

Risk Factors for Kaposi Sarcoma

The following factors can raise a person's risk of developing KS:

- Ethnicity - people of Jewish or Mediterranean descent, as well as equatorial Africans, have a higher risk of developing KS
- Gender – men, generally, have a higher risk of developing Kaposi sarcoma than women
- Human herpes virus 8 (HHV-8) - this virus may be the cause for Kaposi sarcoma to develop. It is also called the Kaposi sarcoma herpes virus (KSHV).
- Immune deficiency - people with HIV/Aids and people whose immune systems are suppressed because of organ transplantation have a higher risk of developing Kaposi Sarcoma.
- Sexual activity - homosexual (active) men tend to have a higher risk of HHV-8.

Zhang, P., Wang, J., Zhang, X., Wang, X., Jiang, L. & Gu, X. 2020.

BACKGROUND: Kaposi sarcoma-associated herpes virus (KSHV) is one of the most common causal agents of Kaposi Sarcoma (KS) in individuals with HIV-infections. The virus has gained attention over the past few decades due to its remarkable pathogenic mechanisms. A group of genes, ORF71, ORF72, and ORF73, are expressed as polycistronic mRNAs and the functions of ORF71 and ORF72 in KSHV are already reported in the literature. However, the function of ORF73 has remained a mystery. The aim of this study is to conduct comprehensive exploratory experiments to clarify the role of ORF73 in KSHV pathology and discover markers of AIDS-associated KSHV-induced KS by bioinformatic approaches.

METHODS AND RESULTS: We searched for homologues of ORF-73 and attempted to predict protein-protein interactions (PPI) based on GeneCards and UniProtKB, utilizing Position-Specific Iterated BLAST (PSI-BLAST). We applied Gene Ontology (GO) and KEGG pathway analyses to identify highly conserved regions between ORF-73 and p53to help us identify potential markers with predominant hits and interactions in the KEGG pathway associated with host apoptosis and cell arrest. The protein p53 is selected because it is an important tumor suppressor antigen. To identify

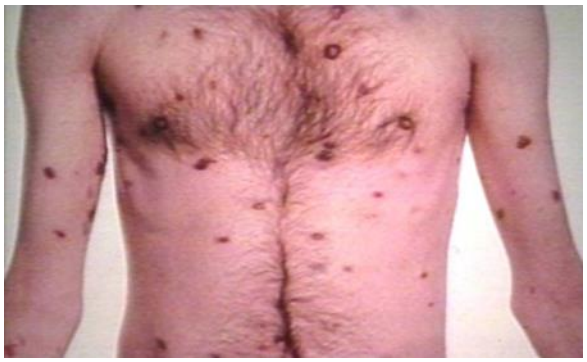
the potential roles of the candidate markers at the molecular level, we used PSIPRED keeping the conserved domains as the major parameters to predict secondary structures. We based the FUGE interpretation consolidations of the sequence-structure comparisons on distance homology, where the score for the amino acids matching the insertion/deletion (indels) detected were based on structures compared to the FUGE database of structural profiles. We also calculated the compatibility scores of sequence alignments accordingly. Based on the PSI-BLAST homologues, we checked the disordered structures predicted using PSI-Pred and DISO-Pred for developing a hidden Markov model (HMM). We further applied these HMMs models based on the alignment of constructed 3D models between the known structure and the HMM of our sequence. Moreover, stable homology and structurally conserved domains confirmed that ORF-73 maybe an important prognostic marker for AIDS-associated KS.
CONCLUSION: Collectively, similar variants of ORF-73 markers involved in the immune response may interact with targeted host proteins as predicted by our computational analysis. This work also suggests the existence of potential conformational changes that need to be further explored to help elucidate the role of immune signaling during KS towards the development of therapeutic applications.

Poizot-Martin, I., Obry-Roguet, V., Duvivier, C., Lions, C., Huleux, T., Jacomet, C., Ferry, T., Cheret, A., Allavena, C., Bani-Sadr, F., Palich, R., Cabié, A., Fresard, A., Pugliese, P., Delobel, P., Lamaury, I., Hustache-Mathieu, L., Brégigeon, S., Makinson, A., Rey, D. & Dat'AIDS study group. 2020.
BACKGROUND: Although antiretroviral therapy (ART) has reduced the risk of Kaposi sarcoma (KS), KS cases still occur in HIV-infected people.
OBJECTIVE: To describe all KS cases observed between 2010 and 2015 in a country with high ART coverage.
METHODS: Retrospective study using longitudinal data from 44 642 patients in the French Dat'AIDS multicenter cohort. Patients' characteristics were described at KS diagnosis according to ART exposure and to HIV-plasma viral load (HIV-pVL) (≤50 or > 50) copies/mL).
RESULTS: Among the 209 KS cases diagnosed during the study period, 33.2% occurred in ART naïve patients, 17.3% in ART-experienced patients, and 49.5% in patients on ART, of whom 23% for more than 6 months. Among these patients, 24 (11.5%) had HIV-pVL≤50 cp/mL, and 16 (66%) were treated with a boosted-PI-based regimen. The distribution of KS localization did not differ by ART status nor by year of diagnosis.
LIMITATIONS: Data on human herpesvirus 8, treatment modalities for KS and response rate were not collected.
CONCLUSION: Half of KS cases observed in the study period occurred in patients not on ART, reflecting the persistence of late HIV diagnosis. Factors associated with KS in patients on ART with HIV-pVL≤ 50 cp/mL remain to be explored.

Signs and Symptoms of Kaposi Sarcoma (KS)
The first symptom of KS is usually skin lesions. Occasionally KS can also affect other parts of the body such as the lymph nodes, lungs, stomach or bowel. When this happens the symptoms will depend on the part of the body that is affected. Some people may have general symptoms such as fever, weight loss and loss of energy.

Skin lesions - these can range in colour from pink to brown, brown-red or reddish purple. KS can appear as a raised or slightly raised bump (nodule) or a flat area on the skin. The lesions can develop quickly. Although there may be a single area at first, it is possible for more than one to appear. Often

the lesions merge to form a larger tumour. Any part of the skin can be affected, including the inside of the mouth.



[Picture Credit: Kaposi Sarcoma Picture]

Lymph nodes (glands) - if the lymph nodes are affected by KS, the nodes may become swollen but this generally causes few symptoms.

Swelling in the arms, legs and elsewhere - KS can cause damage to lymph vessels. These are part of the lymphatic system, which helps fight infection. When the lymph vessels are damaged this can lead to a build-up of fluid in the arms or legs. This is called lymphoedema. There can also be severe swelling of the face and scrotum (in males).

Lung problems - KS in the lungs can cause breathlessness and a cough which may be life threatening.

Digestive system (stomach and bowel) problems - KS may cause symptoms such as feeling nauseas and being sick (vomiting). The patient may also have trouble eating and/or swallowing

Anaemia - occasionally the lesions may bleed slowly, which over a period of time may cause anaemia (low numbers of red blood cells).

Types of Kaposi Sarcoma

There are five (5) main types of Kaposi Sarcoma (KS):

Classic KS - this type of KS is very rare and is usually only found on the skin, mainly on the lower legs and feet. It is most common in older men of Jewish or Mediterranean origin. It is a slow growing cancer and does not usually cause any problems. In the early stages, it does not usually need treatment. If the lesions are large, and in very visible areas on the body, the patient may be given radiotherapy to get rid of it. The doctor may also suggest freezing it with liquid nitrogen or removing it with a small operation.

Endemic or African KS - as the name suggests, this type of KS is found in parts of Africa, where HHV-8 infection is common. It is faster growing than Classic KS. It is more common in men, but women and children of all ages may develop it.

Transplant KS found in people with weakened immune systems – People who have weakened or damaged immune systems are most likely to develop this type of KS, for example, people who have had an organ transplant operation.

Aids related KS - this is the most common and fastest growing type of KS. If someone has Aids, the immune system is weakened. This increases the risk for developing KS.

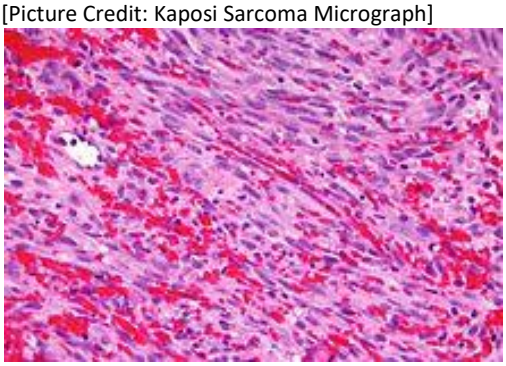
Poizot-Martin, I., Lions, C., Cheret, A., Rey, D., Duvivier, C., Jacomet, C., Allavena, C., Huleux, T., Bani-Sadr, F., Obry-Roguet, V., Makinson, A. & Dat'AIDS study group. 2020.
Objective: Kaposi sarcoma is still observed among people living with HIV (PLHIV) including those on ART with undetectable HIV viral load (HIV-VL). We aimed to assess Kaposi sarcoma incidence and trends between 2010 and 2015 in France and to highlight associated factors.
Design: Retrospective study using longitudinal data from the Dat'AIDS cohort including 44 642 PLWH. For the incidence assessment, Kaposi sarcoma cases occurring within 30 days of cohort enrollment were excluded.
Methods: Demographic, immunological, and therapeutic characteristics collected at time of Kaposi sarcoma diagnosis or at last visit for patients without Kaposi sarcoma.
Results: Among 180 216.4 person-years, Kaposi sarcoma incidence was 76 (95% CI 64.3-89.9)/10 person-years. Multivariate analysis (Poisson regression) revealed the positive association with male sex, MSM transmission route, lower CD4 T-cell count, higher CD8 T-cell count, not to be on ART, whereas HIV follow-up time, duration with an HIV-VL 50 copies/ml or less were negatively associated with Kaposi sarcoma. According to the different models tested, HIV-VL, CD4 : CD8 ratio and nadir CD4 cell count were associated with Kaposi sarcoma. Moreover, stratified analysis showed that patients with a CD4 : CD8 ratio 0.5 or less or a CD8 T-cell count greater than 1000 cells/µl were at higher risk of Kaposi sarcoma regardless of the CD4 T-cell count.
Conclusion: This study showed that in a resource-rich country setting with high ART coverage, Kaposi sarcoma still occurred among PLWH. CD8 hyperlymphocytosis and CD4 : CD8 ratio should be now considered as two useful markers to better identify patients at increased Kaposi sarcoma risk, including those with a CD4 T-cell count greater than 500 cells/µl.

Non-epidemic Gay-Related Kaposi Sarcoma - there is a type of non-epidemic KS that develops in (active) homosexual men who have no signs or symptoms of HIV infection. This type of Kaposi sarcoma progresses slowly, with new lesions appearing every few years. The lesions are most common on the arms, legs, and genitals, but can develop anywhere on the skin. This type of Kaposi sarcoma is rare.

Diagnosis of Kaposi Sarcoma

To be sure that a lesion is caused by KS, the doctor will usually take a small sample of tissue from the lesion and send it to a laboratory to be analysed. This is called a *biopsy*. A specially trained doctor called a *pathologist* can often diagnose KS by looking at the cells in the biopsy sample under a microscope.

[Picture Credit: Kaposi Sarcoma Micrograph]



Micrograph of a Kaposi sarcoma showing the characteristic spindle cells, high vascularity and intracellular hyaline globs. H&E stain.

For skin lesions, the doctor may perform a *punch biopsy*, which removes a tiny round piece of tissue. If the entire lesion is removed, it is called an *excisional biopsy*. These procedures can often be done under local anaesthesia. Lesions in other areas, such as the lungs or intestines, can be biopsied during other procedures such as bronchoscopy or endoscopy.

Other tests may include:

- an oral examination, to check for lesions on the palate, tongue, gums, or tonsils
- a rectal examination, to check for lesions in the anus
- *endoscopy* - *a* procedure to look at organs and tissues inside the body to check for abnormal areas. An endoscope is inserted through an incision (cut) in the skin or opening in the body, such as the mouth. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue or lymph node samples, which are checked under a microscope for signs of disease. This is used to find Kaposi sarcoma lesions in the gastrointestinal tract.
- a *barium enema*, which allows doctors to track the progress of barium through the colon by using X-rays
- *sigmoidoscopy*, which involves using an endoscope or sigmoidoscope to view the lining of the rectum and colon
- chest X-rays, to check for lung lesions
- *computed tomography* (CT) imaging, which looks for lesions or other abnormalities
- *bronchoscopy* - *a* procedure to look inside the trachea and large airways in the lungs for abnormal areas. A bronchoscope is inserted through the nose or mouth into the trachea and lungs. A bronchoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.
- *lung biopsy* - if bronchoscopy shows lesions in the lungs, the doctor can take a sample for microscopic examination.

Staging of Kaposi Sarcoma

Staging is a way of describing where the cancer is located, if or where it has spread, and whether it is affecting the functions of other organs in the body. Doctors use diagnostic tests to determine the cancer's stage, so staging may not be complete until all the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis (chance of recovery).

Treatment of Kaposi Sarcoma

Treatment of Kaposi sarcoma can be difficult due to the immunosuppressed state of many of the people who are affected. These people are at a high risk of infections from procedures. The doctor may recommend treatment based on the patient's general health as well as on where the lesions are, how extensive they are, and how many there are.

Generally, most cancers are treated by physical removal of the tumour or lesion (*cryotherapy* in this case), chemotherapy, radiation, or a combination. For people with Aids, anti-HIV medications are used against the virus. This can improve the person's overall health and help treat Kaposi sarcoma.

For skin lesions, some possible treatments are:

- Cryotherapy - cryotherapy is a procedure that uses liquid nitrogen or other cryogens to freeze tissue. In cases of Kaposi's sarcoma, a doctor might freeze the lesions to destroy them.
- Locoregional therapy - locoregional therapy involves injecting chemotherapy agents directly into the Kaposi's sarcoma lesions.
- Radiation therapy - direct radiation therapy is another option to treat for the lesions. This involves aiming radiation directly at the spots. Some side effects associated with radiation include fatigue
- If the Kaposi's sarcoma has advanced and affects the internal organs, other therapies may be prescribed.
- Chemotherapy: as with many cancers, chemotherapy is an option in treating Kaposi sarcoma.

Beauclair, G., Naimo, E., Dubich, T., Rückert, J., Koch, S., Dhingra, A., Wirth, D. & Schulz, T.F. 2019. "Kaposi's Sarcoma-associated herpesvirus (KSHV) is the cause of three human malignancies, Kaposi's Sarcoma, Primary Effusion Lymphoma and the plasma cell variant of Multicentric Castleman's Disease. Previous research has shown that several cellular tyrosine kinases play crucial roles during several steps in the virus replication cycle. Two KSHV proteins also have protein kinase function: open reading frame (ORF) 36 encodes a serin-threonine kinase, while ORF21 encodes a thymidine kinase (TK), which has recently been found to be an efficient tyrosine kinase. In this study, we explore the role of the ORF21 tyrosine kinase function in KSHV lytic replication. By generating a recombinant KSHV mutant with an enzymatically inactive ORF21 protein we show that the tyrosine kinase function of ORF21/TK is not required for the progression of the lytic replication in tissue culture, but that it is essential for the phosphorylation and activation to toxic moieties of the antiviral drugs zidovudine and brivudine. In addition, we identify several tyrosine kinase inhibitors, already in clinical use against human malignancies, which potently inhibit not only ORF21 TK kinase function, but also viral lytic reactivation and the development of KSHV-infected endothelial tumors in mice. As they target both cellular tyrosine kinases and a viral kinase, some of these compounds might find a use in the treatment of KSHV-associated malignancies.**Importance:** Our findings address the role of KSHV ORF21 as a tyrosine kinase during lytic replication and the activation of prodrugs in KSHV-infected cells. We also show the potential of selected clinically approved tyrosine kinase inhibitors to inhibit KSHV TK, KSHV lytic replication, infectious virions release and the development of an endothelial tumor. Since they target both cellular tyrosine kinases supporting productive viral replication and a viral kinase, these drugs, which are already approved for clinical use, may be suitable for repurposing for the treatment of KSHV-related tumors in AIDS patients or transplant recipients."

Prognosis (Outlook)
The outlook for Kaposi's sarcoma depends on the form of the disease. Milder forms are rare and develop slowly. People with classic KS usually die of other causes or develop a second type of cancer. About one-third of people with classic Kaposi's sarcoma develop another cancer.

Reducing the Risk for Kaposi Sarcoma
While it is not possible to prevent Kaposi sarcoma, a person can significantly reduce his or her risk by avoiding the known risk factors that raises the risk of HIV/Aids infection, especially by avoiding risky sexual practices, such as having unprotected sex and using intravenous (IV) needles that have been used by someone else.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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