



## Review Article

# Kaposi Sarcoma: Clinical Indices and Diagnosis

Chukwunonso Livinus Udeh<sup>1</sup>, Pramod Singh Khatri<sup>2,\*</sup>

<sup>1</sup>Clinical Research, Amity Medical School, Amity University, Haryana, India

<sup>2</sup>Department of Clinical Research, Amity Medical School, Amity University, Haryana, India

## Email address:

lilnons2000@yahoo.com (C. L. Udeh), pramodsinghkhatri@gmail.com (P. S. Khatri)

\*Corresponding author

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**Abstract:** Any type of cancer that originate from the connective tissues are termed Sarcomas. The name Kaposi in relation to Kaposi sarcoma was derived from a Hungarian Dermatologist, Dr. Moritz Kaposi who is the first to describe this kind of tumor. KS is caused by a Herpes virus called HHV-8 or KSHV which is transmitted through unprotected sexual intercourse (higher in MSM), sharing of used needles, blood transfusion and organ transplant. There are five (5) epidemiological types of KS; Classic, Transplant, African, AIDS-related and Non-epidemic gay related. KS is the commonest symptom of an advanced HIV infected patient and its proliferation is faster due to the weakened immune system. Awareness about this sarcoma is poor. This disease is generally diagnosed as brown, red or purple patches/plagues/nodules on the skin, mucosal cavity of the GIT, Lungs and the oral cavity. There are also immunohistochemical staining endothelial markers that are used to differentiate KS from other types of sarcomas. CD31 is best used as an endothelial marker for lesions from HIV+ patients. Some other common markers include CD4, LNA-1, BCL-2 and VEGFR-3. Other symptoms of KS are shortness of breath, internal bleeding Anemia and Fatigue. Highly Active Antiretroviral Therapy (HAART) is believed to be the most efficient treatment for AIDS-related KS. Other soothing treatments available are chemotherapy, topical ointments, cryotherapy, photodynamic therapy, laser therapy and a times excisional surgery. There are active clinical trials towards treatment of KS. Some of which are done by combining different doses of HAART regimen with other therapeutic agents. One of the CTs been conducted by the National Cancer Institute in the U.S is the Phase II/ Phase I study using Pomalidomide in treating HIV and Non-HIV patients with Kaposi Sarcoma.

**Keywords:** Kaposi, Sarcoma, Infection, Lesions

## 1. Introduction

Cancer and its excruciating proliferation is a widely discussed health issue nowadays. Different types of sarcomas have been described. Sarcomas are those cancer types that originate from connective tissues in the body. These tumors are mostly presented in the muscles, bones, tendons, nerves, cartilages, fat, blood vessels of arms and legs. Although, they can happen in any other part. Sarcomas are rare type of cancers. There are over 50 types of sarcomas. These types are DIVIDED into 2 groups; soft tissue sarcoma and bone sarcoma or osteosarcoma [1].

The word Kaposi was coined from a Dermatologist from Hungary named Moritz Kaposi. He was practicing in 1872 at the University of Vienna. He is the 1<sup>st</sup> to describe this type of

Sarcoma [3].

Kaposi sarcoma is a type of sarcoma caused by a viral infection. This virus is titled human herpesvirus 8 (HHV-8 or KSHV), which is one of the seven currently known human viruses that cause cancer. These viruses are generally termed Oncoviruses.

Kaposi sarcoma progress from cells that line the blood or lymph vessels. Eventually, it appears as tumors on the skin surface and on certain mucosal surfaces including the mouth and Gastrointestinal tract. They also develop from other body tissues like the lymph nodes, liver and the lungs. These tumors are seen as abnormal cells of Kaposi Sarcoma in brown, purple or red blotches. The affected areas are generally called Lesions. KS Lesions of the skin are often seen on the face or legs. They usually cause no symptoms. The legions on the legs

and groin can lead to edema of these affected areas. Internal Lesions of the GIT, lungs or liver causes serious medical problems. It can cause internal bleeding and respiratory problems [4]. Before the HIV/AIDS endemic, KS progresses slowly but it is faster in patients with HIV virus [5].

In the 1980s, Kaposi sarcoma became widely known as one of the illnesses used to define AIDS. In 1994, these cancer cause was revealed to be of viral origin [2]. The cause of this cancer is now established, still there is lack of widespread awareness of it among individuals at risk of getting infected by KSHV/HHV-8 [6].

## 2. The Virus

After Dr. Moritz Kaposi description of Kaposi Sarcoma as rare classical structure of idiopathic multiple pigments sarcoma of the skin, Chang and Moore further characterized the DNA fragments of this virus in 1994. They used a method known as representational difference analysis. These fragments were obtained from KS biopsies. They were able to establish a novel human c-herpesvirus association with Kaposi Sarcoma. More than 95% of total lesions of KS contain KSHV viral DNA [7].

The genome of KSHV is double-stranded DNA ranging from 165 to 170 kb. It has a long unique region (LUR) and a terminal repeat (TR) sequences. The LUR is about 138 to 140.5kb in length. It comprises of all the KSHV ORFs. The LUR is sided by the TR sequences at opposite ends making it a linear viral genome. Each TR is 801bp in length and they are maximally rich in guanine and cytosine. There are variations of KSHV isolates because of the number of these TR sequences, ranging from 16 to 75 [8]. This genome is highly similar to rhesus monkey rhadinovirus (RRV) of the rhadinovirus subfamily of c-hetpesvirinae and retroperitoneal fibromatosis-associated herpes virus (RFHV) [7].

KSHV is an encapsulated DNA virus which is large and double-stranded. A protein known as Capsid covers its nucleic acids. This Capsid is enclosed by an amorphous protein layer called the Tegument. The Tegument is then surrounded by a lipid envelope derived from a part of the plasma membrane. KSHV has taken numerous genes from host cells like genes encoding complement-binding protein, BCL-2, IL-6, Cyclin-D; a G protein-coupled receptor, Flice inhibitory protein (FLIP) and interferon regulatory factor. Also some DNA synthesis proteins including DNA polymerase, dihydrofolate reductase, thymidine kinase, thymidylate synthetase and many others [8].

## 3. Types of Kaposi Sarcoma

The Cancer society of South Africa classified Kaposi Sarcoma into five (5) main types;

- a. Classic KS
- b. Endemic or African KS
- c. Transplant KS
- d. AIDS-related KS
- e. Non-epidemic Gay related KS

### f. CLASSIC KAPOSI SARCOMA

This first type of KS is commonly seen in middle aged or elderly patients. It is largely seen in Jewish men, Middle east, Mediterranean region and Eastern Europe. Infections from HHV-8 occurs often in these regions and this virus is likely the cause of CKS in these populations. It can equally be seen less likely in other parts of the world. It occurs mostly in men and the lesions frequently surfaces below the trunk and feet (both toes and soles). KS here is seen as purple, red or deep blue patches that sprouts to enlarged plaques. It grows slowly and doesn't develop any symptom. It does not cause any problem at the early stages. These large plaques can be removed with chemotherapy or fast surgery after being frozen with liquid nitrogen. Individuals with CKS have stronger immune system than those with other types of KS, making the lesions generally develop slower and spread over a longer period [5, 10].

### a. ENDEMIC OR AFRICAN KS

This type of carcinoma is termed "African" because it happens to the inhabitants of Equatorial Africa. Malnutrition, Malaria, HIV and chronic infections often compromise the immune system of humans living in Africa. These contribute to the advancement of KS more broadly in a particular age range than other types of KS. Endemic KS is rare in children but seen in aggressive form when it happens. Individuals younger than 40 years are commonly affected. It often occurs in women than men. Endemic KS easily affect the lymph nodes and body organs. It likely progresses rapidly than classic KS [10, 11].

### b. TRANSPLANT KAPOSI SARCOMA

It is also known as Iatrogenic KS. This type of KS is found in people with weakened or destroyed immune system. Most especially, people that went through an organ transplant surgery. It presents possible visceral lesions seen as localized mucocutaneous or disseminated KS. This KS is rare. Such patients take drugs to prevent their body from repudiating the new organ thereby suppressing their immune system. This situation can be reversed by reducing the dosage or changing the type of immunosuppressant taken. Radiotherapy or chemotherapy can be introduced if the initial method doesn't work [5, 12].

### c. AIDS-RELATED KS

This KS was first described during the highest point of AIDS epidemic in the 1980's prior to the discovery of highly active antiretroviral therapy (HAART). It is the most common of all KS. It surfaces after the immune system of a patient has been weakened by HIV leading to opportunistic infections and development of AIDS. HHV-8 is believed to be sexually transmitted the same way HIV is. Fortunately, HAART declines the incidence of AIDS related KS in HIV-infected population. Then, Kaposi sarcoma was one of the first AIDS-defining illnesses. The lesions vary greatly from other types of KS. They are located on the head and body trunk. Also seen in mucous membranes of the GIT and lungs. AIDS related KS progresses rapidly than other types of KS. It is often aggressive with higher lesions. It is associated with high mortality after hospitalization, although suitable

chemotherapy may induce its regression in patients. It is mostly found in homosexual males and intravenous drug users between the ages of 20-50 years. Women and children are equally affected in Africa [5, 10, 13].

d. NON-EPIDEMIC GAY-RELATED KS

This type of KS is rare and not related to any epidemic. It's

not related to HIV infection. It's mostly seen in active homosexual men (MSM) who have no signs or symptoms of been infected by HIV. Progression is slow with new lesions appearing infrequently. These lesions are commonly seen on the arms, legs and groin. It can equally develop in any others parts of the body. The cases are similar to classic KS [4, 5].

## Typical Lesions Of Kaposi's Sarcoma



*Figure 1. Showing typical lesions of Kaposi Sarcoma.*

### 4. Immunohistochemistry

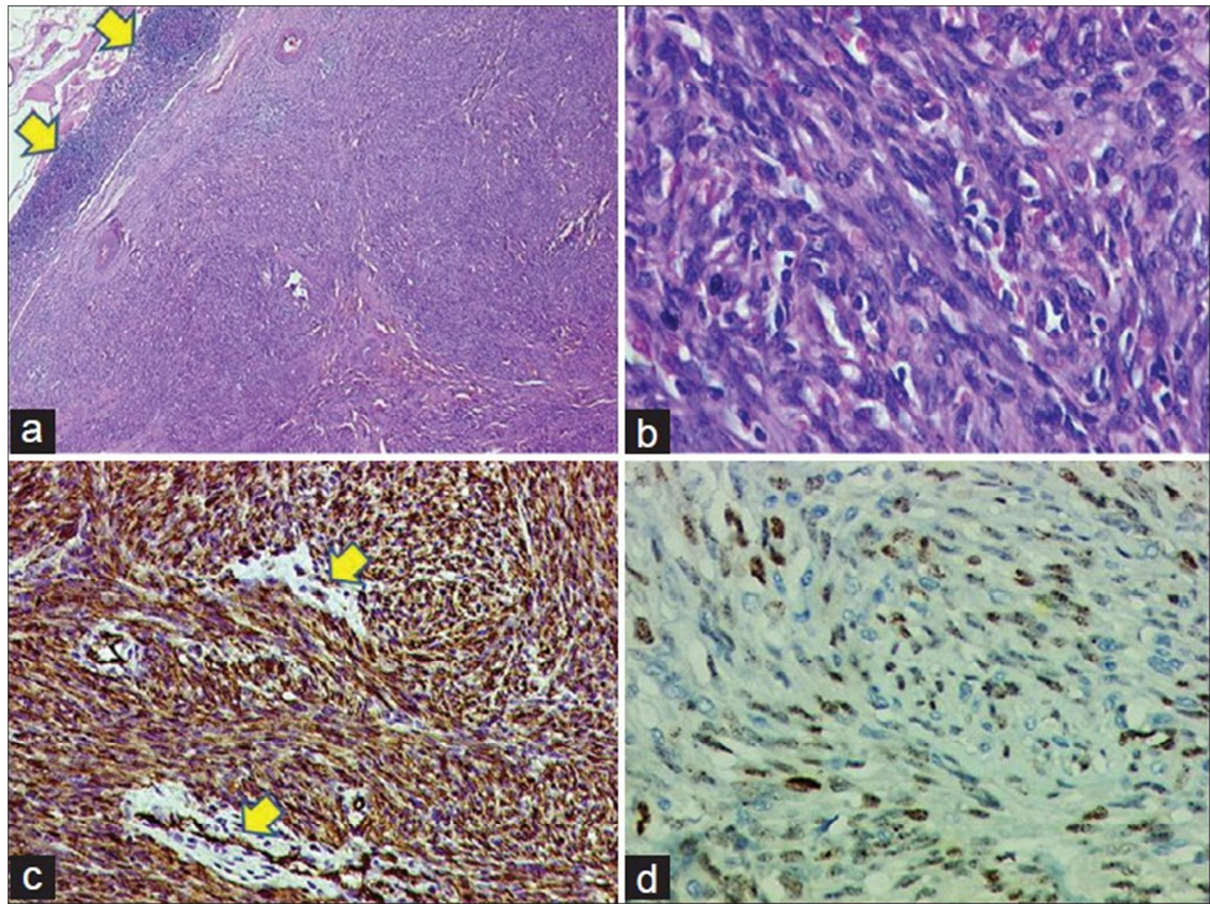
Immunohistochemistry of Kaposi sarcoma has been evaluated with more than one hundred (100) million antibodies. Cells from KS lesions stain positively with many endothelial markers like CD31 (PECAM-1), CD34 and Factor VII-related antigen [12]. Some other markers that have been used for HHV-8 include LNA-1, Cyclin D1, p53, Bcl-2, D240, p27kip1, LYVE-1, VEGFR-3, Prox-1 and FLI1.

LNA-1 is determined to exhibit 100% specificity and sensitivity for diagnosing Kaposi sarcoma in patients. It is most useful in the differentiation of KS from its mimickers. Additionally, Cyclin D1, p53 and Bcl-2 express nether in early stages of KS but highly expressed in its nodular stage. P27Kip1 is highly expressed in the patch/plaque (early) stage in comparison to the tumor stage [14].

In nodular lesions, CD34, D240 and FLI1 sensitivity is higher than that of CD31 in non-AIDS related KS. Despite the fact that CD31 is more specific for immunochemistry of KS, it exhibits weaker immunoreactivity in comparison with CD34. This is because a protein called K5, also known as MIR2 which has the same morphology to cellular

membrane-associated RING-CH (MAPRCH) protein removes CD31 from KSHV infected endothelial cells. This intervenes with the lysosomal degradation and internalization of the platelet-endothelial cell adhesion molecule. So, the KSHV modulatory function enables the evasion from the host's inactive immune response and may also impart the abnormal spindle cell function. Using CD31 as a specific marker for KS will result to a lower diagnostic sensitivity than other endothelial markers associated with KSHV infections in vascular lesions of the sarcoma [15]. CD31 staining is highly positive for AIDS-related KS and less for CD34. Particularly in the lymph node of an HIV-positive individual, the presence of vascular pattern and spindle shaped cells are useful in diagnosis which should be supported with Immunohistochemical HHV8 markers [16]. HHV8 is not only limited to KS. It has been detected in some dermatofibromas, angiosarcomas and hemangiomas [17]. In the evaluation of problematic vascular proliferations, the immunohistochemistry of LNA-1 is preferred over the polymerase chain reaction detection of HHV8. This is because the contamination of mononuclear inflammatory cells can harbour this virus especially in HIV+ patients [12].





**Figure 2.** A and B: conventional hematoxylin and eosin stain sections from lymph nodes exhibiting moderate degree of nuclear atypia with several mitotic figures with plasma cells interspersed. C and D: Positively diffused immunohistochemical stains of CD31 and HHV8, weakly positive for CD34 [16].

## 5. Histopathology

Multiple histopathological features of KS have been described. They are not mutually exclusive and may have overlapping features. They include Patch, nodular, plaque, lymphadenopathic, infiltrative, inflammatory, florid, telangiectatic, ecchymotic, keloidal, angiomatous, anaplastic, lymphangiomatous and generalized lymphedema.

The patch stage is characterized by proliferation of many uneven vascular spaces in the dermis which is parallel to the epidermis. These vessels are slit-like and present around pre-existing blood, skin adnexa and collagen fibers. Erythrocytes and hemosiderin may be present outside the vessels. These features are similar to a granulation tissue.

In the plaque stage, the spindle cells are more prominent. There is a dermal proliferation with poorly differentiated slit-like blood vessels. Eosinophilic globules are present with prominence of Hemosiderin.

The nodular stage is well defined by prominent interlacing bundles of spindle cells surrounding a slit-like blood vessels and extravasation of erythrocytes. These features are more prominent than the earlier stages. Other characteristics include mitosis, dilated thin walls at the periphery and eosinophilic hyaline globules.

Lymphangiomatous-like KS lesions have a bulla like

appearance characterized by penetration of dermal collagen by irregular anastomosing vascular channels surfaced by a flattened epithelium. Anaplastic variation of KS has been reported in Africa; Malawi and Uganda. Its features include nuclear pleomorphism, greater cellularity and frequent mitotic activity [18].

There are minor histopathological differences between AIDS-related KS and non-HIV associated KS. Mitosis and cellular anaplastic features are more common in non-HIV associated KS, whereas more extensive dissecting vessels are seen in AIDS-KS. The lesions of KS contain hemosiderin laden macrophages because iron is important in its pathogenesis. Iron staining can be used to differentiate KS from non-iron containing resembling interstitial granuloma annular lesions. Nodular/advanced stages are PAS- positive and stain bright red with Mallory's trichrome [12, 18].

## 6. Other Symptoms

Together with the colored patches, plaques or nodule KS is seen as, the American cancer society mentioned symptoms that can arise.

- a. If the lung is affected, it can cause shortness of breath and bleeding which can cause the patient to be coughing out blood.

- b. In the case of GIT, it can cause abdominal pain, diarrhea, black, tarry or bloody stool due to loss of RBCs.
- c. Anaemia
- d. General body Fatigue [4].

## 7. Diagnosis

Typical pathological findings are used to determine the definitive diagnosis of Kaposi sarcoma. Biopsy of a lesion of the skin is required and for the organs, it's done by GI endoscopy, pleural or trans bronchial biopsy. Cutaneous KS may not occur alongside Gastrointestinal KS. Esophagogastroduodenoscopy or colonoscopy is used to observe such lesions. Because of the submucosal locations of these lesions, the yield of the biopsy may be low. Chest radiograms also demonstrate the diffuse, reticular-nodular infiltrates, mediastinal enlargement and maybe, pleural effusions. Thallium or Technetium 99 mm scanning is used to differentiate between KS and similar pulmonary lesions such as lymphomas and infections, which are typically gallium-avid [19].

There are four stages in diagnosing KS;

- a. Clinical and medical history of patient is taken in detail including sexual orientation, history/level of exposure.
- b. Physical examination of the lesions in the mouth, rectum, groin, lymph nodes, lymphatic organs and any other part of the skin.
- c. Routine blood tests: used to detect abnormalities like anemia and low WBC. HIV test is also done because HIV infection is the most common cause of KS. Also CD4 count is done.
- d. Skin lesions are taken for biopsy. Bronchoscopy is prescribed if lesions are suspected in the lungs. Upper endoscopic examination is done if there are presence of GIT lesions. A Sigmoidoscope is inserted through the anus to examine the lower intestine and computerized tomography (CT) scan is run to examine the presence of any lesion in any other part of the body [20].

Differential diagnosis of various KS types is large. In some clinical settings, patch-stage needs to be differentiated from fibrous histiocytoma, hemosiderotic hemangioma and interstitial granuloma annulare. Some lesions might be confused to another, examples; nodular KS, vascular tumors like spindle cell hemangioma and Kaposi form hemangioendothelioma, fibrohistocytic tumors (angiomatoid, cellular and atypical variants of fibrous histiocytoma and dermatofibrosarcoma protuberans), spindle cell melanoma, dermal fasciitis and many other spindle cell mesenchymal neoplasms are similar. Higher forms and eruptive forms of KS should always be differentiated from angiosarcoma. There should be a differentiation between paucivascular anaplastic KS and other high grade melanomas. Melanoma may be mimicked by pigmented anaplastic KS. The architectural arrangement of telangiectatic KS may mimic a sinusoidal hemangioma which is an uncommon acquired variant of cavernous hemangioma. A true keloid scar from a previous biopsy may be mistaken to be Keloidal KS. Pyogenic

granuloma-like KS may be misdiagnosed as a true Pyogenic granuloma (lobular capillary hemangioma), mostly when the surface is traumatized and ulcerated. The differential diagnosis of intravascular KS includes intravascular papillary endothelial hyperplasia, intravenous PG, intravascular fasciitis, papillary intralymphatic angioendothelioma (also called Dabska tumor), and intravascular myopericytoma. Misdiagnosis of Regressed KS lesions may be taken, clinically and histologically as pigmented purpuric dermatitis without any prior knowledge of response to therapy. Immunohistochemistry using vascular markers (CD31 or CD34) and/or lymphatic markers (D2-40) is not as specific as LNA-1 in diagnosing KS for most of the above mentioned vascular individual units [12].

## 8. Treatment

There are lots of available treatments for reducing KS. AIDS-related KS can be reduced or if possible, cured permanently using HAART. Effective regimens of antiretroviral therapy can wipe KS maximally [21]. Not enough data exist on the comparative efficacy of various HAART regimens in the treatment of KS. Though its noted that experimental models and anecdotal data may support the sole usage of protease inhibitor-containing regimens [22]. Invitro model of KSHV showed that replication can also be inhibited using many antiviral agents like ganciclovir, foscarnet and cidofovir. AVR therapy with cidofovir targeted towards KSHV is not yet effective for treatment of KS, maybe because of the little amount of lytic KSHV present in KS tumours [23, 24]. Limited localized KS lesions can be treated with chemotherapy, topical ointments, cryotherapy, photodynamic therapy, laser therapy and a times excisional surgery. Extensive lesions that can't be treated with chemotherapy can be treated with radiation therapy. Fast proliferating, extensive cutaneous and/or visceral KS should be treated with systemic therapy (some involving cytotoxic chemotherapy). Some FDA approved chemotherapeutic agents are 2 liposomal anthracyclines (pegylated liposomal doxorubicin and liposomal daunorubicin) and taxane paclitaxel [21].

## 9. Active Clinical Trials

Some active trials conducted by the National Cancer Institute in U.S.A to treat Kaposi Sarcoma include:

- a. Phase II and Phase I trial using Pomalidomide in treating HIV and Non-HIV patients with Kaposi Sarcoma. Safety, efficacy, tolerability and pharmacokinetics of oral dose of Pomalidomide is studied under regimen of 5mg/day for 21days of a 28day cycle. In the case of initial dose not tolerated, Pomalidomide is assessed at 3mg/day for 21days of a 28day cycle. Other objectives of this CT is to explore in a preliminary manner the antitumor effects of Pomalidomide at any of the above described doses and assess the quality of life of the subjects. Also assess the pharmacokinetics of Pomalidomide in relation to

common ARV agents; especially those that can cause nephrotoxicity such as Tenofovir and explore in a preliminary manner the safety, tolerability and antitumor effect of a second course of Pomalidomide in patients who manifest KS again after benefiting from the initial treatment with Pomalidomide. This trial is ongoing at National Institute of Health Clinical Centre, Bethesda, Maryland.

- b. Phase II study using Pegylated liposomal doxorubicin hydrochloride and Bevacizumab towards treating patients with advanced KS i.e. patients whose KS has spread all over the body and usually cannot be cured or controlled with treatment. At the induction phase, Bevacizumab is given intravenously over 90minutes on day 1 and over 60minutes on day 8 of course 1, and over 30minutes on day 1 of courses 2-6. Pegylated liposomal doxorubicin hydrochloride is also given over 30mins on day 8. This treatment is repeated every 3week for up to 6 courses if the disease is not progressing and therapy is non-toxic. The maintenance phase commences when Patient's disease is stable, partially responsive or completely cured. They are given Bevacizumab IV over 30minutes on day 1. Treatment is repeated every 3weeks for up to 11 courses if there is no disease progression or toxicity.
- c. EphB4-HAS clinical trial in treating Patients with Kaposi Sarcoma
- d. Use of Nivolumab and Ipilimumab in treating Patients with HIV Associated metastatic solid tumours and unresponsive to Surgery.
- e. Pomalidomide and Pegylated Liposomal Doxorubicin Hydrochloride in treating Patients with Advanced or Refractory Kaposi Sarcoma.
- f. Natural History of Zidovudine and Valganciclovir or Rituximab and Pegylated Liposomal Doxorubicin Hydrochloride in treating Patients with Kaposi Sarcoma-Associated Herpes Virus [25].
- g. Some active CTs in other countries include:
- h. Phase I and II trial of selumetinib combined with AVR therapy for AIDS-related Kaposi Sarcoma, conducted at Sheffield, United Kingdom.
- i. Cell therapy of Human herpes virus (HHV) specific immune effector (IE) cell therapy for HHV-related diseases in China [26].
- j. Phase I and II Study of Oral MEK Inhibitor Selumetinib (AZD6244 Hyd-Sulphate) in combination with HAART in AIDS-related Kaposi Sarcoma (KS) also in UK [27].

## 10. Discussion

Any form of Kaposi sarcoma is caused by Human Herpes Virus 8 (HHV-8). This virus is transmitted through unprotected sexual intercourse (higher in MSM), organ transplant and sharing of used injection needles. The AIDS-related KS is the most widely known effect of advanced HIV infection patients. There are five types of KS in relation to its epidemiological attributes. They can be seen as patches,

plaques and nodules. Immunohistochemistry of Kaposi sarcoma has been evaluated with more than one hundred (100) million antibodies. Cells from KS lesions stain positively with endothelial markers like CD31 (PECAM-1), CD34 and Factor VII-related antigen [10, 12]. Some other markers that have been used for HHV-8 include LNA-1, Cyclin D1, p53, Bcl-2, D240, p27kip1, LYVE-1, VEGFR-3, Prox-1 and FLI1. CD31 staining is highly positive for AIDS-related KS and less for CD34. Particularly in the lymph node of an HIV-positive individual, the presence of vascular pattern and spindle shaped cells are useful in diagnosis which should be supported with Immunohistochemical HHV8 markers [16]. Pentatowitx *et al* stated some level of differential diagnosis of KS because a lesion can be confused as another e.g Higher forms of KS can be confused to be Angiosarcoma [12]. There are lots of treatments for KS. HAART is used to reduce or if possible cure the AIDS-related sarcoma [22]. Clinical trials are ongoing towards better treatment and improving the wellbeing of patients with KS. Some of which are listed in this review article.

## 11. Conclusion

Kaposi sarcoma has been a relevant health issue even before the onset of HIV/AIDS epidemic. The virus HHV-8 is not restricted to this disease alone. It is unfortunate that there is less awareness of this virus and its attributed diseases. This disease presents as purple, red and brown patches/plagues/nodules on the skin; known as Lesion. It can also be seen in the mucosal areas of oral cavity, lungs and GIT. Differential diagnosis is important in diagnosing the type and stage of this sarcoma before commencing treatment. This critical review showed that the five types of this cancer is not restricted to HIV positive individuals. KS is still the most common symptom of an advanced HIV+ patient. Numerous immunohistochemical stains are available for the virus. It's important not to restrict the lesions to only one type of staining because each histologic subtype react differently to all stains. Many cancer research centers in different countries are undergoing clinical trials, some done with combination of HAART and different therapeutic agents to determine any most safe and effective treatment for this disease.

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