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Advances in the Study of Kaposi's Sarcoma in Human

Mohammad Salim

Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. Univ., Rewa (M. P.), India.

ABSTRACT

Kaposi sarcoma (KS) is a kind of cancer that is widespread all over the world. This is for the first time discovered by Hungarian physician and dermatologist Moritz Kaposi in 1872 as a skin tumor. The name Kaposi sarcoma was coined to honour of the discoverer. Kaposi sarcoma is caused by the Kaposi sarcoma herpesvirus (KSHV). This is soft tissue cancer of blood vessels and lymphatic system developing purplish-red coloured lesions mostly in mouth, face, nose, genitals, and the lower extremities. The KSHV is easily transmitted either sexually or via the act of parturition vertically. There are 4 types of Kaposi's sarcoma distributed globally such as chronic or European, endemic or African, transplant-associated or iatrogenic and AIDS-related or epidemic. Italians using topical steroids are more prone to have this type of cancer. The KSHV has been isolated in almost all cases of Kaposi's sarcoma cancer. KS is composed of spindle shaped cells and inflammatory mononuclear cells. These cells grow faster and survive for a longer period of time. The various stages of Kaposi's sarcoma are maculonodular stage, infiltrative stage, florid stage and disseminated stage. The KSHV has also been found to be associated with two other lymphoproliferative diseases such as primary effusion lymphoma (PEL) and multicentric Castleman's diseases. Kaposi's sarcoma is an outcome of viral infection. As this is not a curable disease, it can often be treated for many years. And, public awareness about KS can only save the lives properly. However, currently, the drug used to treat Kaposi's sarcoma are thalidomide, bevacizumab, and sirolimus.

Keywords: Human Herpes Virus-8, Kaposi Sarcoma, Cancer

INTRODUCTION

Moritz Kaposi was a Hungarian physician and dermatologist who described a kind of skin tumor initially in 1872 that received his name later as Kaposi sarcoma (KS).¹ In fact, it was Sternberg who gave the name as Kaposi sarcoma in 1912.² But, it took nearly more than 100 years we discovered the causal organism of Kaposi's sarcoma as HHV-8 in 1994.³ This is a kind of indolent angioproliferative spindle cell tumor cancer developed from endothelial and immune cells under the skin and soft tissues caused by the human herpes virus-8 or Kaposi's sarcoma herpesvirus (KSHV).³⁻⁵ KS is a multicentric vascular tumor of mesenchymal origin derived due to the hyperplasia affecting the blood vessels developing on soft tissues in multiple areas of the entire body at once.⁶⁻¹⁰

Further, as the Kaposi's sarcoma herpesvirus (KSHV) is easily transmitted either sexually via blood and saliva or vertically through parturition, the act of childbirth from mother to her baby,¹¹⁻¹⁷ it may lie dormant or replicated to cause cancer

in human. This has usually been observed that the persons who are immunocompetent can carry the load of KSHV without any problem, but it triggers the Kaposi's sarcoma in immunocompromised individuals. This is most commonly developed in either immunodeficient or the patients kept under immunosuppressant medications.^{18,19} The present review on Kaposi's sarcoma is prepared in the light of recent researches done so far in the field of viral origin of cancer. In the present review, clinical presentation, histopathology, stages and the types of Kaposi's sarcoma with the treatment of the same disease have been discussed as under :

CLINICAL PRESENTATION

Clinically, there are four types of Kaposi's sarcoma developed in human as chronic or European, endemic or African, transplant-associated or iatrogenic and AIDS-related or epidemic Kaposi's sarcoma.^{20,21} The diagnosis of Kaposi's sarcoma is based on the visual inspections of characteristi-

Corresponding Author:

Dr. Mohammad Salim, Professor, Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. Univ., Rewa (M. P.), India.

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cally colored, cutaneous, non-itchy, painless and even non dangerous spots appeared on skin. These spots are red or purple on white skin and blue brown or black on dark skin. These lesions are found on face including nose, around the eyes, ears and lips; oral cavity including gingiva, palate, tongue and buccal mucosa and the lower extremities or lower limbs. Early on, these lesions are usually painless but when bleed or ulcerated over time become painful. Most specifically the lesions present in the areas of legs or groin may cause the feet to swell moving very painfully.¹⁹⁻²³

Further, these lesions are also found on some internal organs, especially on the lungs and the gastrointestinal tract. If the virus infects the lungs, it often quickly gets worse, causing respiratory failure and death.²² Similarly, the infection taking place in digestive system shows no symptoms at all except the pain in the stomach until it becomes very advanced. In an advanced stage, intestinal obstruction, bleeding and bloody stool may come out during defecation. But, despite all these complications, a patient suffering from gastrointestinal Kaposi sarcoma looks like as normal as was being before 5 years of infections. It means that even after 5 years of diagnosis a person with KSHV looks like a normal average person. And, it all happens due to the differential medications provided to the patient that often responding well in time.²³⁻²⁵

In addition, the patients suffering from Kaposi's sarcoma may also show some associated symptoms such as swollen lymph nodes, cough, fever, fatigue, loss of appetite, weight loss, edema in foot, nausea, painful stomach, and vomiting. Similarly, the KS life-threatening conditions may also occur as difficult swallowing, intolerable belly pain with bloody defecation, intestinal blockage, severe swelling in upper and lower limbs, face or scrotum, severe coughing and the shortness of breath.²⁴

Sometimes, the lesion of KS also arises as a systemic inflammatory condition due to the physical stimuli precisely at the site of trauma such as injury, surgical or other wounds is characteristically known as koebner's phenomenon. The etiopathology of this phenomenon is not yet known. Although, this is a rare phenomenon in connection with KS; the koebnerization has also been documented in several other skin diseases, including vitiligo, psoriasis, lichen planus, and viral warts.²⁵

Histopathology of the Disease

The histopathology of Kaposi's sarcoma shows red cells in slit like spaces formed by atypical spindle cell proliferation of endothelial and associated inflammatory cells. These cells grow faster and survive for a longer period of time. The KSHV has been isolated in almost all the cases of Kaposi's sarcoma cancer.^{5,26,27} The KSHV proteins in cancer cells and Periodic-acid-Shiff (PAS) reagent positive hyaline bodies are also seen in the cytoplasm.^{9,28}

Stages of Kaposi's sarcoma

Depending upon whether the Kaposi's sarcoma is localized, external, internal, or immunosuppressed, there have been various attempts to classify the stages of Kaposi's sarcoma.^{26,29,30-32} On the basis of lesions in lymph nodes, the stages of disease distribution and the clinical pace of progression, the Kaposi's sarcoma is further diagnosed histologically as under:

Stage I Maculonodular stage

Small macules and nodules are confined to appear only on the lower extremities.

Stage II Infiltrative stage

The plaques are formed on the same lower extremities. Sometimes, they are still associated with small nodules.

Stage III Florid Stage

Often ulcerated angiomatous multiple plaques and nodules are found.

Stage IV Disseminated Stage

Multiple angiomatous nodules and plaques extending beyond the lower extremities.

Types of Kaposi's sarcoma

Epidemiologically, the Kaposi's sarcoma can primarily be categorized into four types ranging from minimal mucocutaneous lesions to extensive organ involvement. The different types of KS are based on different populations it captured in, but changes within the KS Cells are more or less similar²⁰. They are of four types given as under:

1. Sporadic, classic (Mediterranean), European, chronic type of Kaposi's sarcoma.
2. Endemic, African Lymphadenopathic type of Kaposi's sarcoma.
3. Transplant associated (Iatrogenic) Immunocompromised Kaposi's sarcoma.
4. Epidemic, AIDS related Acquired Immuno deficient Kaposi's sarcoma.³³⁻³⁸

Sporadic, classic (Mediterranean), European, chronic type of Kaposi's sarcoma

This type of KS is primarily occurred in the eastern European population, Ascanajee Jews and Mediterranean descent.³⁹⁻⁴² Elderly men with weak immunity between 50 to 70 years of age are more affected than female.³⁷ Chronic Kaposi's sarcoma usually has silent, protracted or indolent course and is usually limited to the skin. It slowly progresses over many years and often is not the cause of death. As this is non-aggressive and slow growing KS, the lesions do not grow as quickly, and new lesions do not develop as often. They have solitary, one or more lesions on legs ankles or soles⁴⁸.

Italians using topical steroids are more prone to have this type of cancer.³⁴ Skin lesions are mostly found on the distal lower extremities or lower limbs. This form of disease rarely has lymph node, mucous membrane or visceral involvement. Oral mucosa is sometimes affected. In addition, the visceral lesions are usually asymptomatic and discovered only by autopsy. Clinically, gastrointestinal bleeding may occur. Approximately, one third of same KS patients may also develop another malignancy in future as non-Hodgkin lymphoma.⁴³⁻⁴⁷

Endemic, African, Lymphadenopathic type of Kaposi's sarcoma

This is an endemic African type of Kaposi's sarcoma mainly found in males under the age of 40, mostly in countries of Malawi, Uganda, Swaziland, Zambia and Zimbabwe.⁴⁹ Quite a good number of children of both sexes (approximately 70%) before attaining the age of puberty have also been reported to develop the KS with absolute mortality within three years. It has also been observed that in all these cases, only visceral nodes were affected. The cutaneous lesions were all absent in children but may appear in adults. The malaria and malnutrition prevalent in the region have also been reported to play some role in developing the KS as it weakens the children's immunity severely.⁵⁰⁻⁵⁵

Transplant associated (iatrogenic), Immuno-compromised Kaposi's sarcoma

Kaposi's sarcoma is also developed in those who have undergone solid organ transplantation receiving immunosuppressive therapy like the excessive use of cyclosporin A medication.^{55,56} It usually develops within two years of organ transplantation. This is an aggressive type of cancer affecting the lower distal extremities, visceral organs, and lymph nodes. However, the individuals born with congenital immunodeficiency are not at the elevated risk of developing Kaposi's sarcoma.⁵⁷⁻⁶⁰ Recently, a new drug named sirolimus has given rather better results acting as antitumor and immunosuppressant both at a time.⁴⁵ As this kind of KS affects the people who have had undergone organ transplantation taking immunosuppressive drugs to slow down their immune system, this is now being observed that lowering the dose of immunodrugs makes the KS lesions either go away or get smaller. The greater the immunosuppression, the more extensive and aggressive KS will be.⁴⁶⁻⁴⁸

Epidemic, AIDS-related Acquired Immunodeficient Kaposi's sarcoma

Another type of Kaposi's sarcoma is a type of cancer that people with AIDS often get. Here KS is an AIDS defining condition. It means that an HIV positive person suffering from KS is definitely has progressed to AIDS. But, on the other hand, a person having been suffering from KS may not be suffering from AIDS. KS can also develop in an other-

wise healthy person as well.⁴⁹ This is clinically most aggressive and common opportunistic malignancy in HIV patients worldwide, occurring mostly in Africa and the USA. In the 1980s, AIDS related KS was very common in the USA. Similarly, this has also been one of the most common cancers in Uganda and Zambia, especially in children. The risk groups are gay and heterosexual men and women. But, it remains prevalent amongst men who have sex with men.^{19,50-52} All of them were HIV positive. But, now a very different type of Kaposi's sarcoma has also been developing in male homosexuals who are HIV negative.

Since the KSHV is an oncogenic virus, the AIDS related KS has gained much attention due to its abnormal pathogenicity in human. It has been observed that at least three genes are responsible for the cause of KS in AIDS patient. They are named as ORF71, ORF72, and ORF73. With both localized and disseminated cutaneous involvement, the AIDS related KS often initially involves the lymph nodes, which is later on disseminated to various parts of the viscera. Generally, the pulmonary and gastrointestinal mucocutaneous lymph nodes are involved.^{22,23} Oral Kaposi's sarcoma in acquired immunodeficiency syndrome have also been reported.⁵⁷ In the early 1980s, KS was one of the most frequent malignancies reported in AIDS patient before the introduction of antiretroviral therapies.²⁵ Further, in United States, treating the HIV patients with highly active antiretroviral therapy (HAART) has resulted in the fewer cases of AIDS associated KS but in rest parts of the world where HAART services are not easy to provide, KS in AIDS patients have advanced quickly.⁵⁸ Kaposi's sarcoma has rarely been reported from India. The first case of AIDS related KS from India was reported in 1993, and since then only 16 cases have been reported.⁵⁹⁻⁶¹

TREATMENT OF THE DISEASE

Unfortunately, there is nothing available at present as treatment to kill the KSHV absolutely, instead of only alleviating the symptoms to slow down the disease progression. Similarly, there is no any routine method for identifying the KS in an individual except the antibody test.⁶²⁻⁶⁵ Nowadays, KS diagnosis in lesion specimens usually requires not only histological and immunohistochemical characterization but also HHV-8 detection using new molecular biology.²⁵ Similarly, an oncologist and cancer expert can only identify the lesions present on the body. This is also quite unfortunate for us that sometimes a patient himself do not require any treatment as initially the lesions are otherwise painless. One of the oldest drugs to treat the lesions of Kaposi sarcoma is thalidomide. The drug has helped in shrinking the lesions of KS.⁶⁶ But, as the drug has got some serious side effects, the other drugs like lenalidomide and pomalidomide are being studied for the same purposes.⁶⁷⁻⁶⁹ Angiogenesis inhibitors blocking the growth of blood vessels within tumors may also treat the le-

sions of KS. The drug named bevacizumab is one of them²⁰. The other drugs like sirolimus and everolimus are being studied further.⁶⁷⁻⁷⁰

Further, the treatment options are more or less found similar to those recommended for other types of cancer such as surgical excision⁷⁰, radiation⁷¹, chemotherapy⁷², electrochemotherapy to use electric impulse in injecting the chemo drugs into tumors effectively^{73,74} such as vincristin^{75,76} vinblastin⁷⁷, Vincalucoblastin⁷⁸, bleomycin⁷⁶ and doxorubicin.⁷⁶ Other treatment modalities are cutaneous cryosurgery⁷⁹, cryotherapy in which the lesions are frozen using liquid nitrogen⁸⁰, use of cytokine inhibitors⁶⁸, immunotherapy including interferon, antiviral medications including Zidovudine, ganciclovir, Valganciclovir, cidofovir, and the topical application of alitretinoin gel (Panretin).⁸⁰⁻⁸⁵

In addition, it has also been observed that some specific drugs commonly used for cancers are also being studied for use against Kaposi's sarcoma such as paclitaxel⁸⁶, docetaxel⁸⁷ and imatinib.⁸⁸ Similarly, antiretroviral therapy has also been found to be the best way to treat the Kaposi's sarcoma. It has not only even clear up the skin lesions but to have lowered the cases simultaneously.⁸⁹⁻⁹¹ While infection of KSHV in human is estimated to account for nearly >44000 new cancer cases and 20,000 deaths globally every year, their efforts to develop vaccines are limited.⁹²⁻⁹⁵

Since Kaposi sarcoma is not a curable disease, it could be treated to a limited extent to control the symptoms. The choice of treatment modalities depends upon the extent of the disease. Though it often progresses slowly, KS can ultimately be fatal. One should always seek treatment for KS. Further, as the indolent KS appears usually in older people taking many years to develop and grow, many people die of some other parainfections before their KS becomes serious enough to be fatal. Similarly, as the AIDS related KS is now treatable and not a cause of death by itself, we should nothing more to worry about it except to be alert in the future.⁹²⁻⁹⁵

PERSPECTIVES

Kaposi sarcoma is a rare, slow growing tumor cancer that develops underneath the skin with reddish-purple or blue-brown in colour lesions. These lesions are mainly found on the face, nose, legs, and around the anus. Some internal organs, especially the lungs and gastrointestinal tract are also affected. The gastrointestinal tract lesions are typically symptomless. Rarely, they may lead to bloody stools, pain, diarrhea or physical obstruction. But, the lung infection usually causes breathlessness due to blockage. A lung bleeding lesion may leak blood with mucus, which the individual then coughs up.^{96,97,98}

Kaposi's sarcoma herpesvirus (KSHV) has been isolated in nearly all patients tumor suffering from the same cancer. This is spindle cell tumor thought to be derived from endothelial cell lineage. It arises as a cancer of lymphatic endothelium in vascular channels which are filled with blood cells giving the tumor its characteristic bruise - like appearance. The highly vascular network of KS tumor leaked R.B.C. in the surrounding tissues causing the tumor black in colour developing the inflammation and pain in the lesions.⁹⁹⁻¹⁰²

Further, there are four types of Kaposi sarcoma that have so far been described in literature they are European or classic, endemic or African, transplant-associated and AIDS-related. Generally, it has been observed that Kaposi's sarcoma is more linked to either immunocompromised patients infected with AIDS or had undergone organ transplantation taking immunosuppressive medications. The HHV-8 virus has also been found to be involved in producing some rare cancer like a blood cancer known as primary effusion lymphoma and multicentric Castleman disease.⁹⁹⁻¹⁰⁰ This is a sexually transmitted virus but can also be spread by some other ways also as direct contact through blood and saliva. Since, all forms of KS are manifested in the oral cavity; the KSHV is more easily being transmitted via saliva as well.^{16,17}

CONCLUSION

Cancer is an outcome of viral infection. It starts as a chronic inflammation (Kapositis) which ultimately produce Kaposi sarcoma. KS is a relatively large, linear double-stranded DNA tumor virus¹⁰¹ that transforms the cells in such a way that it multiplied indefinitely to live longer which eventually develops to form cancer, but it does not mean that all infected individuals will develop the cancer, appearing that some other factors are also required for it to develop.^{8,98} We opined, as the KS has a variable course and is not curable, it can possibly be treated and controlled symptomatically for a longer period of time. Finally, we should promote the public awareness using media for early detection and diagnosis of Kaposi's sarcoma, especially in Africa.¹⁰²

Abbreviations

KSHV	-	Kaposi's sarcoma herpes virus
AIDS	-	Acquired immune deficiency syndrome
KS	-	Kaposi's sarcoma
PEL	-	Primary effusion lymphoma
MCD	-	Multicentric Castleman's disease
HHV	-	Human herpesvirus
PAS	-	Periodic-acid-Shiff reagent
HIV	-	Human immunodeficiency virus
HAART	-	Highly active antiretroviral therapy
RBC	-	Red blood corpuscles
DNA	-	Deoxyribonucleic acid

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