

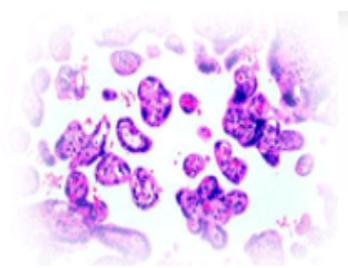
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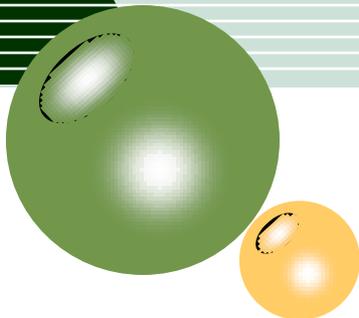
# Pathology of Kaposi Sarcoma

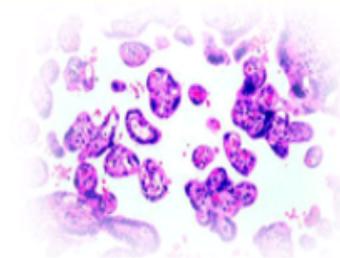
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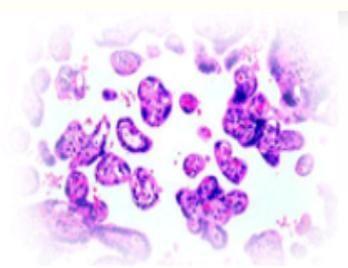
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## Pathology of Kaposi Sarcoma

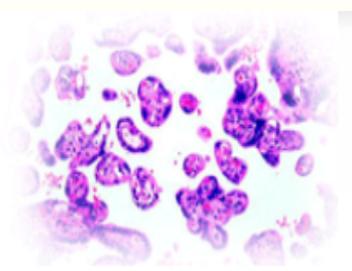
Kaposi's sarcoma (KS) is an angio-proliferative spindle cell neoplasm of low grade malignancy, described by Moritz Kaposi in 1872. It may be solitary or multifocal. It originates almost from lymphatic endothelium and it was considered rare until the discovery of the Acquired Immunodeficiency Syndrome (AIDS).



## Types of KS

Currently four types are recognized: classic, endemic, epidemic and iatrogenic.

Despite the fact that each of them has a distinct progress, they all have in common the participation of the human herpes virus type 8 (HHV-8) or the Kaposi's sarcoma associated herpes virus (KSHV), although other factors are necessary for the occurrence of the disease.

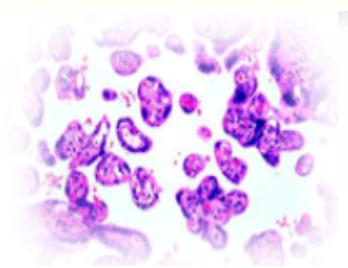


## 1. Classic (indolent) KS:

The classic (indolent) KS is seen in white older men of Southern Mediterranean or Eastern European heritage (over 60 years old in 90% of the cases) and is not related to HIV infection.

The disease initiates as violaceous or reddish brown maculae and papules on the feet or hands, progressing to the legs (most common site) and arms. In 10% of the cases there is involvement of viscera and mucosa.

It progresses over many years and is not often fatal.



## 2. Endemic (African) KS :

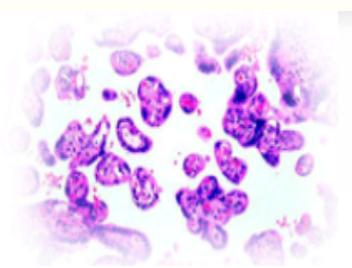
The endemic KS is divided into two subtypes:

### a. African Cutaneous KS

It develops in middle age adults (25 to 50 years old) from tropical Africa, can involve bones, causes legs to swell, and has only local aggressiveness.

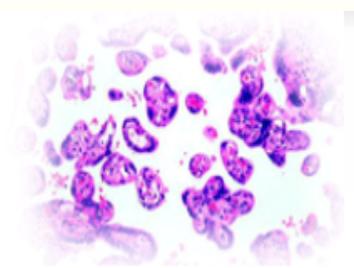
### b. African Lymphadenopathic KS

It develops mainly children from the “Bantu” ethnicity less than 10 years old. It is characterized by generalized lymphadenopathy and has an aggressive clinical behavior, killing within two years after the diagnosis.



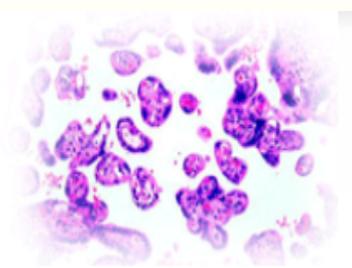
## 3. Epidemic (AIDS associated) KS:

AIDS was described in 1981, in patients where the KS was the main element of the syndrome, observed in 30 to 40% of them. This form of KS develops predominantly in homosexuals and bisexuals, being rare in injectable drug users and heterosexuals. Due to the changes on the sexual behavior and the antiretroviral drugs, its frequency went from 40% at the beginning of the 90ties to 15% nowadays. AIDS associated KS starts as small, non-itchy, slightly painful, violaceous patches first around the head and neck, trunk, limbs and oral mucosa, with subsequent progression to plaques and nodules. Visceral lesions are frequent and gastrointestinal and pulmonary involvements are common. It advances very rapidly, but is not always fatal.



## 4. Iatrogenic (immunosuppression) KS:

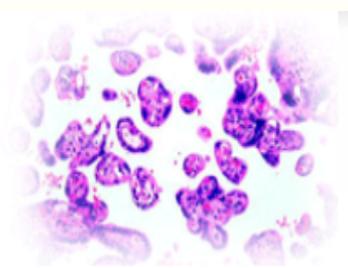
The KS associated with immunosuppressive states develops mainly in *solid organs transplant receivers*, but also in those with *neoplastic diseases* and those with *autoimmune conditions* under immunosuppressive treatment. The clinical and morphological aspects are similar to the classic form. The suspension of the immunosuppressive treatment usually causes the regression of the lesions, but increases the risk of losing the transplant.



## Pathogenesis

Various cofactors have been implicated in the pathogenesis of KS, including genetic susceptibility, immunologic alterations, and endocrine factors.

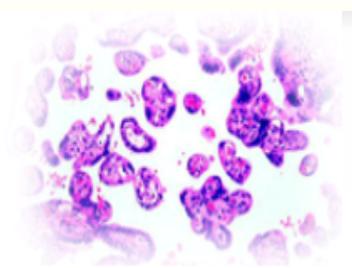
Human herpes virus 8 (HHV-8) also known as Kaposi sarcoma-associated herpes virus (KSHV) is believed to be a major causative factor for all clinical variants of KS. The mechanisms linking infection with this virus to the vascular lesions are unknown.



## Pathogenesis (cont.)

One hypothesis is that HHV-8 infects lymphatic endothelial or other cells. The 165 kb HHV-8 genome is notable for molecular mimicry of several genes homologous to human cellular regulatory genes that are likely to contribute to the pathogenesis of KS through complex interactions with human immune and endothelial systems and promotion of cellular survival and proliferation.

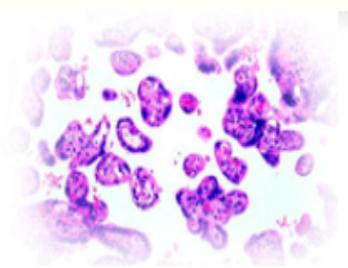
KSHV proteins may disrupt the control of cellular proliferation and prevent apoptosis of endothelial cells, through the production of p53 inhibitors and a viral homologue of cyclin D.



## Pathogenesis (cont.)

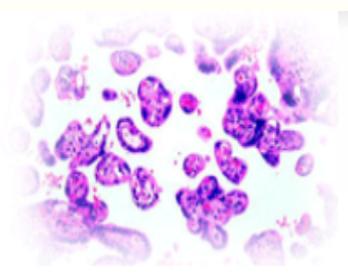
In AIDS associated KS, the HHV-8 induced effects concert with cytokines produced by HIV-infected immune cells, to stimulate proliferation of the vascular cells.

However, classic KS may arise subsequent to other malignancy (often of the reticuloendothelial system). This primary malignancy may precede, coincide with or follow the occurrence of classic KS, offering the suggestion of a common etiology.

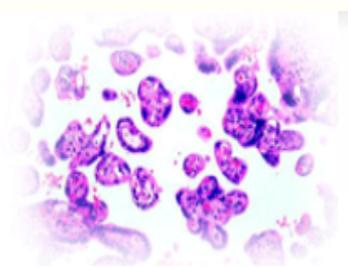


## Gross pathology and disease distribution

Cutaneous lesions of KS usually arise as multicentric neoplasm evidencing as slow progressing multiple vascular cutaneous raised red or purple macules or patches. The lesions could acquire nodular characteristics when the disease progresses. Lesions may be limited to skin or sometimes arises to oral cavity or other mucosal surfaces as mucosal nodules. Lymph nodes or viscera may be involved. The gastrointestinal tract is the most common extracutaneous site of involvement. Other visceral organs that may be affected include liver, heart and lungs.

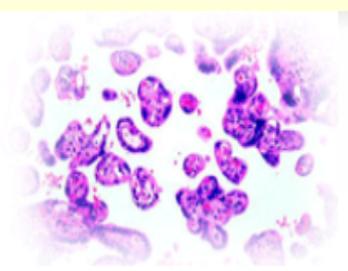


**Gross appearance of different Kaposi Sarcoma lesions including multicentric patch and nodular cutaneous and oral mucosal lesions.**



## Microscopic features

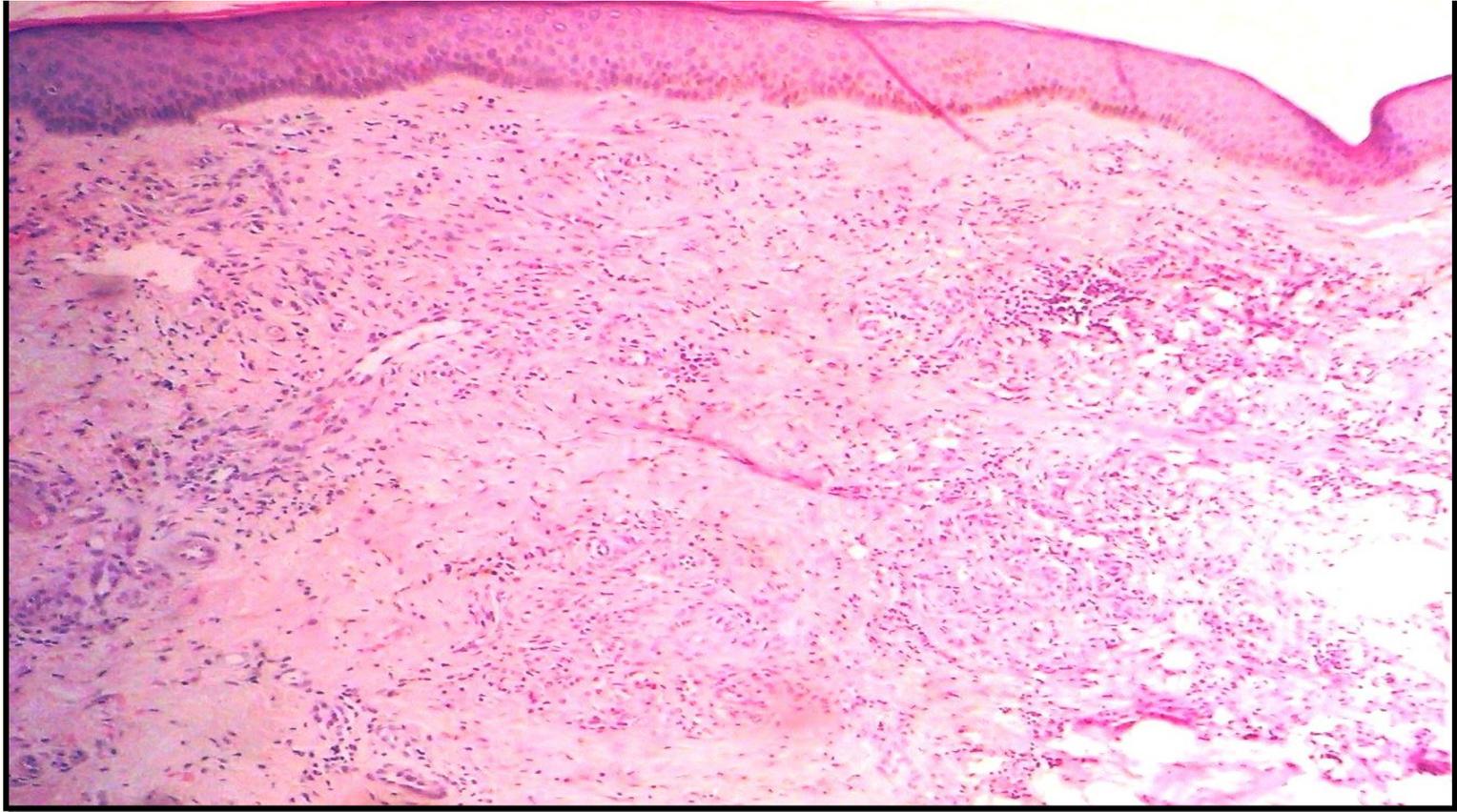
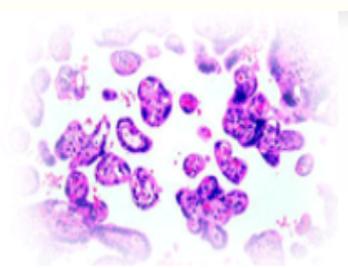
The tumor reveals proliferation of spindle cells (that are mostly latently infected with KSHV) arranged in fascicles with interspersed vascular channels filled with red blood cells. Tumors are distinguished by inflammatory infiltrates, extravasated red blood cells, hemosiderin-laden macrophages and leaky vasculature. Occasional PAS-positive diastase-resistant hyaline globules may be seen. Pleomorphism is usually minimal and mitosis is occasional. The hyaline globules and spindle cells are positive for CD34. Early lesions are difficult to distinguish from granulation tissue.



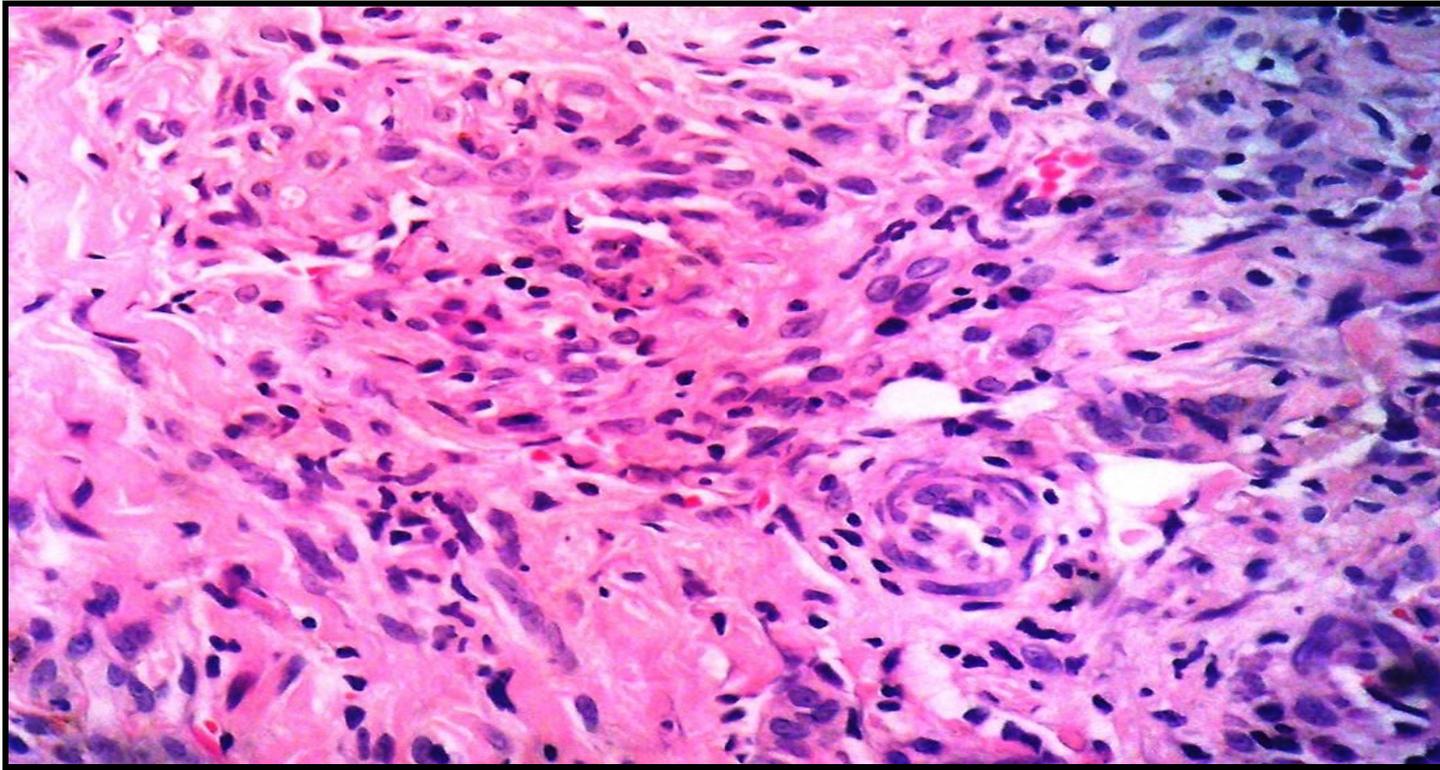
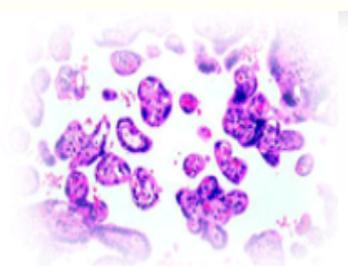
## Microscopic features (cont.)

The microscopic pictures provided here are for a Kaposi's sarcoma lesion from a middle age male patient who was receiving chemotherapy for a malignant lymphoma then developed a cutaneous patch lesions in the arm which was biopsied and sent to our laboratory for histopathologic examination.

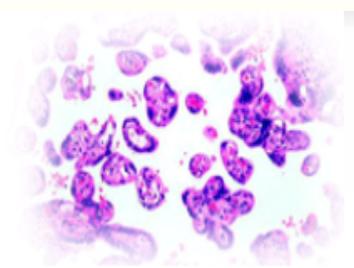
Moreover, the serologic assessment for the patient confirmed his HHV-8 positive serostatus.



**Histopathology shows ill-defined vascular proliferation in the dermis (H&E, x100).**

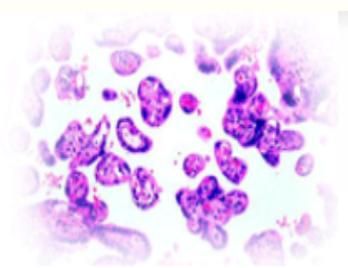


The tumor is composed of proliferating spindle cells with interspersed vascular channels filled with red blood cells. Note the inflammatory infiltrate, extravasated red blood cells and the hyaline globules (H&E,x200).



## How do diagnose KS?

1. **Histopathologic examination of tissue biopsy is mandatory for diagnosis.**
2. **HHV-8 serostatus determined by detection of antibodies to viral lytic antigens by indirect immunofluorescence, combined with the detection of specific antibodies to the K8.1 HHV-8 protein by ELISA.**
3. **Serum testing for antibodies to HIV, using ELISA and Western Blot.**
4. **Chest radiography.**
5. **When clinically indicated, gastrointestinal endoscopy and abdominal ultrasound or computerized tomography (CT).**



## Staging Systems for KS

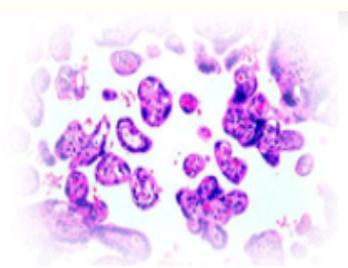
There is no officially accepted system for staging Kaposi sarcoma. However Mitsuyasu classification system is the most simple and clinically acceptable system which comprises 4 stages:

Stage I: Localized nodular Kaposi sarcoma in elderly men

Stage II: Localized, invasive, and aggressive Kaposi sarcoma (mostly seen in Africa)

Stage III: Disseminated mucocutaneous Kaposi sarcoma in African children and patients who are homosexual

Stage IV: Stage III with visceral involvement

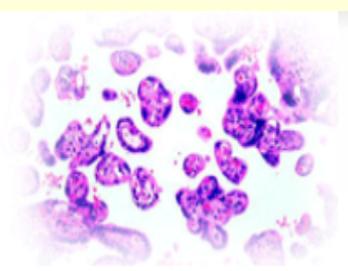


## Prognosis of KS?

Prognosis appears to correlate with the degree of immunosuppression and older age among classic KS patients. Clinical classification of KS may be the best prognosticator, comparing localized nodular disease, locally aggressive disease, and generalized KS. Because indolent KS appears in the elderly and takes many years to develop, many patients die of another condition before their KS becomes serious enough to be fatal.

African KS appearing in young children are the most serious. Left untreated, these forms can result in death in a few short years.

Despite the fact that it is associated with AIDS, AIDS-related KS is most commonly treatable and not fatal.

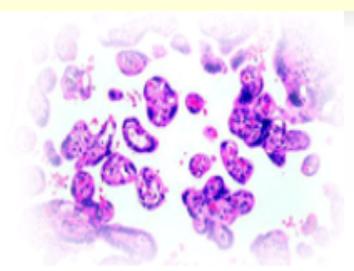


## How to treat KS?

Even though it often progresses slowly, KS can ultimately be fatal, so it should always be treated.

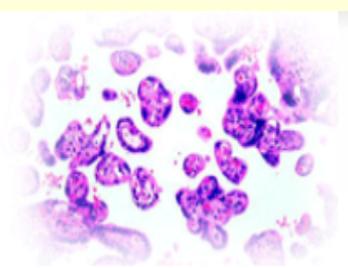
There are several ways of treating KS, including:

1. Surgical excision for small single or few localized tumors,
2. Cryotherapy,
3. Electrodesiccation,
4. Chemotherapy (doxorubicin lipid complex),
5. Interferon (an anti-viral agent), and
6. Radiation (in treating KS when the lesions are not spread over a large part of the body).



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