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Kaposi's Sarcoma

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Authors: Franz A. Mosthaf, Stefan Esser

1 Summary

Kaposi's sarcoma (KS) most likely originates from lymphatic endothelial cells, and human herpesvirus 8 infection contributes to their malignant transformation. Immunosuppression fosters the occurrence, persistence, and progression of KS, which belongs to the most common AIDS-defining neoplasms in HIV-infected individuals. KS is rare among the general population. Advanced, extensive KS can usually be improved clinically and controlled long-term with systemic chemotherapy. Smaller localized manifestations can be treated intralesionally, surgically, or with radiotherapy. In HIV-infected patients, starting antiretroviral therapy, resulting in immune reconstitution, and in immunosuppressed patients, the reduction of immunosuppressive drugs may lead to healing of KS.

Other soft tissue sarcoma entities are addressed in separate Onkopedia guidelines, see Onkopedia Soft Tissue Sarcomas, Onkopedia Gastrointestinal Stromal Tumors (GIST), and Onkopedia Ewing Sarcoma. For further recommendations, we also refer to the S1 guideline Kaposi's sarcoma of the AWMF [1] and the European guideline from EDF/EADO/EORTC [18].

2 Basics

2.1 Definition and background information

In 1872, Moriz Kaposi, a Hungarian dermatologist, described five patients with aggressive idiopathic pigmented sarcoma of the skin ('sarcoma idiopathicum multiplex hemorrhagicum') [15]. One of these patients died of gastrointestinal hemorrhage 15 months after the emergence of the skin lesions. Biopsies showed visceral spread to the lungs and the gastrointestinal tract.

Five different epidemiological/clinical variants have been described, which occur in specific populations or have different manifestations or rates of progression [1, 18]. These variants are thought to represent different clinical courses based on the same pathomechanism.

2.2 Epidemiology

2.2.1 Classic Kaposi's sarcoma

Classic KS primarily affects older men (m:w approx. 15:1) of Eastern European-Mediterranean or Jewish origin with an age peak in the 7th decade of life. Multiple, reddish-bluish-brown plaques and nodules are often found, especially in the lower extremities. The overall course is not markedly progressive over years or decades and rarely involves other organs. Sometimes lymphedema or hyperkeratosis are found.

Histologically, there are infiltrates of spindle-cell endothelia, slit-like new thin-walled, partly incomplete blood vessels with erythrocyte extravasations and hemosiderin deposits, furthermore a lymphocytic inflammatory infiltrate.

2.2.2 Endemic Kaposi's sarcoma

Since the middle of the last century, an increasing incidence of KS in sub-Saharan Africa has been reported. In 1971, KS accounted for 3% to 9% of all cancers in Uganda. In 1983, a dramatic increase in the incidence of KS was reported in Zambia. Once the acquired immunodeficiency syndrome (AIDS) could be reliably diagnosed, it was possible to distinguish HIV-negative endemic Kaposi's sarcoma from HIV-positive epidemic KS. Four clinical courses are described for African endemic KS:

1. relatively benign: nodular skin lesions similar to those seen in classic KS. This mainly affects young men around the age of 35;

2. aggressively localized: cutaneous form of progression with infiltration into soft tissue and bone with fatal outcome within 5 to 7 years;

3. diffuse: mucocutaneous involvement and visceral involvement;

4. fulminant course: lymphadenopathy and involvement of visceral organs usually without skin involvement, occurring preferably in young children.

2.2.3 Iatrogenic immunosuppression-associated Kaposi's sarcoma - epidemiology

KS has been described as a consequence of iatrogenic immunosuppression, usually associated with organ transplantation, but also in other types of immunosuppression. In this regard, there appears to be an increased risk in certain ethnic groups, which are also at increased risk for classic KS. Although the course can be both chronic and rapidly progressive, remission usually occurs after cessation of immunosuppressive therapy.

2.2.4 Epidemic or AIDS-associated Kaposi's sarcoma - epidemiology

In 1981, Friedmann-Kien et al. described fifty previously healthy young homosexual men with KS, affecting lymph nodes, visceral organs, mucosa and skin. At the same time, life-threatening opportunistic infections were present in association with a massive defect in T-cell-mediated immunity. Shortly after that, this disease was described as Acquired Immunodeficiency Syndrome (AIDS) and HIV infection was proven to be the cause. Although the incidence of Kaposi's sarcoma has now decreased significantly as a result of effective antiretroviral therapy for HIV infection, this tumor remains the most common AIDS-associated malignancy in the United States. The same is true for Germany [13]. Overall, the risk for HIV patients to develop KS is increased by 20,000-fold compared to the normal population and by 300-fold compared to other immunosuppressed patients [2]. Among the different HIV transmission groups, the risk of developing KS is 20-fold higher in homosexual men than in patients with hemophilia. KS rarely occurs in women.

In recent years, an increasing number of HIV-associated KS have also been reported in patients with higher T helper cell counts and low HIV viral load, including patients on successful cART (combined Anti-Retroviral Therapy) [26].

At first diagnosis - usually in HIV-infected persons who have not yet received antiretroviral treatment - a multilocular manifestation is typically present. The characteristic skin lesions may develop within a few days. They begin as macules in the skin cleavage lines and progress to

papules or papular tumors. Before the cART era, oral lesions were found as the primary manifestation in many patients, but lesions on the penis were also typically found.

While the skin lesions can be highly stigmatizing for the affected patient, organ involvement is clinically most relevant. Since almost all organs, including the entire gastrointestinal tract, but also the heart, liver and lungs can be affected, life-threatening complications may rapidly emerge. Involvement of the CNS and the eyes is rare.

2.2.5 Kaposi's sarcoma in MSM without HIV infection

In recent years, KS has been increasingly reported in younger HIV-negative men who have sex with men (MSM) from geographic regions with low HHV-8 seroprevalence (e.g., France, England, or Germany) [10, 17, 21].

Similar to classic KS, the course is rather indolent, lesions occur on the entire integument, whereas visceral or organ involvement is very rare. CD4 cell count and CD4/CD8 ratio seem to correlate with disease severity. Because of these features and differences from the previously 4 recognized subtypes of KS, this form is newly classified as an additional (5th) epidemiologic subtype [5, 6].

2.3 Pathogenesis

The pathogenesis of KS is increasingly well understood. Using molecular biology methods and PCR-assisted in situ hybridization, the detection of DNA sequences of a human herpesvirus designated as KS-associated (KSHV) or HHV-8 was achieved in endothelial cells and spindle cells in both AIDS-associated KS and KS from HIV-negative patients in >95% of cases [19, 24]. Therefore, HHV-8, which can be transmitted sexually but also via saliva and blood, is considered to play a crucial role in the development of KS. HHV-8 is not only regularly found in KS, but also in certain B-cell lymphomas ('body cavity-based large B-cell lymphoma') and in multicentric Castleman's disease, but not in other vascular tumors. In addition, leukocytes infected with HHV-8 as well as KS cells were found in the peripheral blood of HIV-positive KS patients. In some regions, e.g., in Italy or Central Africa, HHV-8 is also detectable in up to 50% of the normal population. Probably like other herpesviruses, HHV-8 is transmitted predominantly by saliva, but also sexually, vertically, and via blood.

For the development of KS, HHV-8 is a necessary, but not sufficient condition on its own. Cofactors include the HIV-TAT (trans-activator of transcription) gene and cytokines such as interferon-γ and vascular endothelial cell growth factor (VEGF). Genes with oncogenic properties (c-myc, bcl-2) (transforming, chemoattractant, growth-promoting, anti-apoptotic) and others affecting adherence, cell growth, inflammation, and angiogenesis have been identified in the genome of HHV-8. Expression of these gene products in KS spindle cells in vivo contributes critically to KS development.

4 Clinical characteristics

4.1 Symptoms

KS mainly affects the skin and mucous membranes. Mostly symmetrical on the distal extremities, initially indurated reddish-brown to purplish-red macules often appear in the course of the skin cleavage lines, transforming into extensively infiltrated plaques and hardened painful nodules. Spread is in proximal direction, increasingly disseminated with frequent mucosal involvement. Spontaneous regressions result in hemorrhagic hyperpigmentation, and hemorrhages result in perilesional discoloration (ochre yellow purpura). KS may immure regional lymphatic

structures, causing edema up to elephantiasis-like swelling in the affected drainage area. Mechanical stress and trauma may cause ulcerative rupture, especially affecting the feet.

Internal organs such as lymph nodes, gastrointestinal tract, liver, lungs, kidney and spleen may also be affected. Lymphatic or visceral involvement sometimes occurs without skin involvement.

The course of KS is highly variable, ranging from single lesions that remain stationary for years to markedly aggressive courses that lead to death within a few weeks, especially in HIV-infected individuals.

5 Diagnosis

5.2 Diagnostics

5.2.1 Primary work-up

A stepwise diagnostic approach is recommended. It starts with confirming the diagnosis, see Table 1, followed by staging procedures, see Table 2.

Table 1: Diagnostics for new-onset symptoms and clinical suspicion

Procedure	Note
Medical history and clinical examination	
Biopsy	Cytological diagnosis is usually not sufficient.
HIV test	Mandatory

Table 2: Staging procedures

Procedure	Note
Abdominal ultrasound	First choice method
Thoracic radiography	First choice method
Thoracic computed tomography	Supplementary in case of clinical or imaging suspicion of thoracic organ involvement
Abdominal computed tomography	Supplementary in case of clinical or imaging suspicion of abdominal organ involvement
Endoscopy of the gastrointestinal tract	Supplementary in case of clinical or imaging suspicion of gastrointestinal involvement with therapeutic consequences
Bronchoscopy	Supplementary in case of clinical or imaging suspicion of lung involvement with therapeutic consequences

5.3 Classification

5.3.1 Subtypes of Kaposi's sarcoma

1. Sporadic, classic KS
2. KS associated with iatrogenic immunosuppression
3. Endemic, African KS
4. Epidemic, HIV-associated KS
5. KS in men who have sex with men (MSM) without HIV infection.

5.3.1.1 Histology

KS is a mesenchymal tumor of blood vessels and lymphatic vessels. The histologic image of KS is multifaceted and changes with clinical progression. KS consist of three components [8]:

1. Angiomatous phase
2. Spindle cell phase
3. Inflammatory phase

5.3.1.1.1 Spot (patch) stage

Closely adjacent to larger plexus vessels in the mid and upper stratum reticulare of the dermis, multicentric discrete perivascular spindle cell proliferations with slit-like clefts accompanied by lymphoplasmacytic infiltrates, extravascular erythrocytes, hemosiderin deposits, and siderophages ('pseudogranulomatous pattern') are found in early KS, initially omitting the papillary body and its vessels. In addition, endothelium-lined vascular clefts with empty lumina may dominate. Adnexa and preexisting vascular structures are partially encompassed by the newly formed vascular clefts and lacunae in a semi-island-like fashion ('promontory sign'). In early KS, mitoses and endothelial apoptosis are rare, and cellular and nuclear atypia are absent.

5.3.1.2 Plaque stage

Spindle cells encroaching on the papillary body intersperse the entire corium bundled into short, cell-rich fascicles or strands. Sieve-like, the spindle cell aggregates are broken up by slit-like erythrocyte-rich clefts.

The tumor periphery is dominated by congested, dilated, serum-free vessels engorged with erythrocytes that appear stuffed ('stuffing'). Spindle cell apoptosis but no significant nuclear atypia is observed. Intracellularly and extracellularly, erythrocytic degradation is present in the form of hyaline PAS-positive globi ('hyaline globules').

5.3.1.3 Node or tumor stage

Mitotic-rich, densely packed, factor XIIIa positive, CD31 positive, and CD34 positive, fascicular-structured spindle cell tumors with enclosed erythrocyte-rich clefts, moderate nuclear atypia (exceptionally marked atypia in anaplastic equatorial African variants) often surrounded by an epithelial collerette in exophytic growth, and by a connective tissue pseudocapsule in expansive nodular variants. PAS-positive hyaline erythrocytic globi and apoptotic spindle cells occur in clusters. Older lesions show necrosis in addition to hemorrhages and iron storage.

At regression, a plasma cell-rich, inflammatory round cell infiltrate develops.

5.3.1.4 Immunohistology

Molecular detection of KS herpesvirus HHV-8 is helpful for differential diagnosis.

5.4 Prognostic factors

Prognostic factors are summarized in the TIS (Tumor, Immune system, Systemic Illness) classification of the ACTG (AIDS Clinical Trials Group) [15], see Table 3.

Table 3: TIS classification of ACTG [15]

|	Criteria		
Prognosis	**Tumor characteristics**	**Immune system**	**Systemic involvement**
Favorable	Skin/lymph node involvement only (minimal palate involvement)	CD4 ≥200/µl	No opportunistic infection, no B symptoms, and Karnofsky Performance Score ≥70%
Poor	Tumor with edema or ulceration, extensive oral involvement, organ involvement other than lymph nodes	CD4 <200µl	Opportunistic infections, other AIDS-defining diseases, B-symptomatic or Karnofsky PS <70%

5.5 Differential diagnosis

Differential diagnosis of KS should include acroangiodermatitis in chronic venous insufficiency, other angiosarcomas, hemangiomas, bacillary angiomatosis, Gougerot-Blum disease, melanoma metastases, and erythema elevatum et diutinum. In case of doubt, an excisional biopsy should be performed to confirm the histological diagnosis.

6 Therapy

6.1 Treatment structure

The treatment approach is based on the four epidemiologic clinical variants [1, 17]. An overview of the primary therapeutic procedures is summarized in Figure 1.

Figure 1: Treatment algorithm for Kaposi's sarcoma
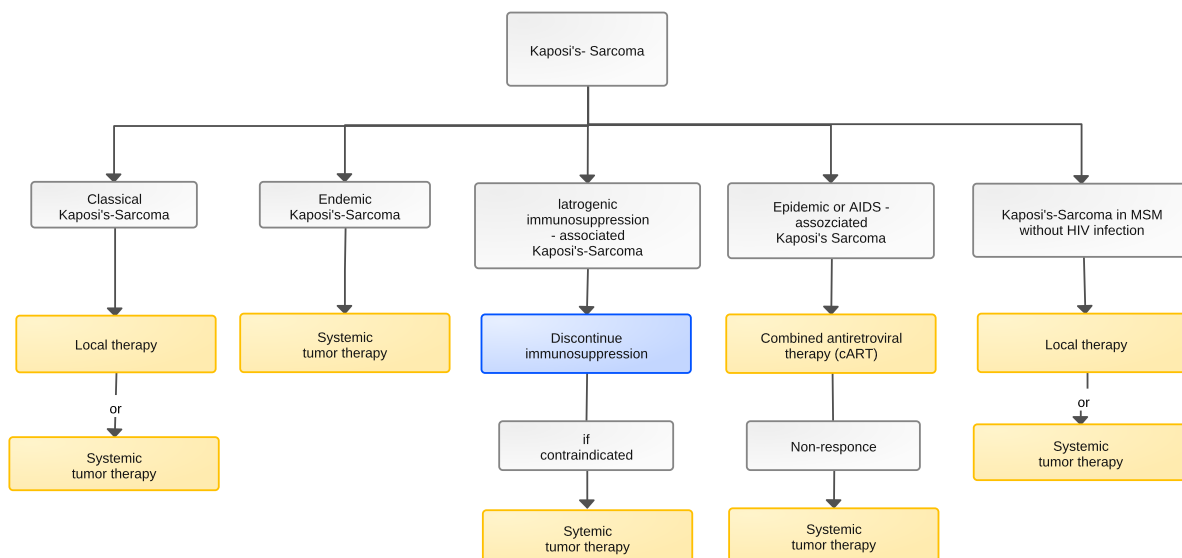
Legend:
━━━ curative intent; ━━━ non-curative intent

6.1.1 Classic Kaposi's sarcoma

In classical KS, individualized treatment concepts and often only local therapy are preferred due to the typically higher age of the patients [22]. Since KS is radiosensitive, fractionated soft X-ray therapy, irradiation with fast electrons or cobalt irradiation are suitable [11]. Cryotherapies may also be used locally, as well as intralesionally applied vinca alkaloids, bleomycin, or interferons [4, 20]. Excision should be considered only in cases of functionally compromising changes and rapid need for action. Systemic chemotherapy, usually with pegylated liposomal

doxorubicin, is indicated for extensive primaries, systemic involvement, and progressive courses [12, 23].

6.1.2 Endemic Kaposi's sarcoma

The endemic African KS usually responds well to systemic therapy, with the exception of the lymphadenopathic variant.

6.1.3 Iatrogenic immunosuppression-associated Kaposi's sarcoma

In iatrogenic immunosuppression-associated KS, tumor lesions usually regress completely after cessation of immunosuppression.

6.1.4 Epidemic or AIDS-associated Kaposi's sarcoma

In epidemic AIDS-associated KS, initiation of combined antiretroviral therapy (cART) in previously non-antiretrovirally treated patients often leads to an arrest of progression or even complete disappearance of the sarcoma lesions [7]. Therefore, antiretroviral therapy should be initiated at the latest with the occurrence of KS in HIV patients. The type of cART does not play a crucial role in KS response, but rather its virologic efficacy and cART-related immune reconstitution. In some cases, a transient, often substantial worsening of the condition may occur as part of the immune reconstitution syndrome. These patients should be treated additionally with systemic chemotherapy. Also, in cases of concurrent new diagnosis of advanced KS with organ involvement and HIV infection, concurrent initiation of antiretroviral and systemic KS therapy as described below is also recommended. If KS is diagnosed in patients already receiving antiretroviral therapy, its effectiveness should be reviewed and eventually be optimized using resistance testing.

6.2 Therapy modalities

6.2.1 Systemic tumor treatment

Regardless of the clinical course, progressive KS should be treated systemically. In the past, a variety of substances were used for this purpose. These include interferon, vinca alkaloids, bleomycin and anthracyclines [9].

Standard therapy for AIDS-associated or advanced KS consists of administration of pegylated liposomal doxorubicin at a dose of 20 mg per m² of body surface area at two to three weeks intervals until complete clinical remission. Generally, clinical follow-up is scheduled at 2-3 months. In case of good regression of tumor lesions without complete remission, further course is awaited after 4-6 months.

As with any initiation of anthracycline therapy, cardiac evaluation with echocardiography should be performed to determine left ventricular ejection fraction, as there is a risk of cardiotoxicity in addition to myelotoxicity. Painful macular erythema (palmoplantar erythrodysesthesia) may occur on the hands and feet associated with the administration of liposomal doxorubicin. However, this side effect is rarely observed at the doses recommended for KS, and more often at higher single doses.

The taxane paclitaxel is available for second-line therapy. In the original report by Gill et al., a dose of 100 mg/m² every two weeks was used [25]. However, since weekly administration at reduced doses has now been shown to be better tolerated and at least as effective in other diseases such as breast carcinoma, weekly administration may also be discussed in KS, see Onko-

[pedia Female Breast Cancer](). Myelotoxicity, alopecia, and onychodystrophy should also be noted. Interactions with cART should be considered in HIV-infected patients with KS.

In HIV-associated KS, systemic interferons can be used alternatively if CD4 cell counts are good (>350 cells/µl) or immune status is good. Pegylated interferons (weekly administration possible, better tolerated than classical interferons) are not approved for KS, but may be more effective and easier to administer, as shown by case reports in AIDS-associated, but also in classical Kaposi's sarcoma [16].

6.2.2 Local treatment options

For local compromising (feet, face) KS lesions, local surgery or local drug application are often sufficient. These are inexpensive and well tolerated. Recurrence in the scars is common after surgical excision. KS are radiosensitive, so radiotherapy may also be used, preferably fractionated single doses of soft X-rays [8]. Other local therapies range from camouflage to intralesional injection of vincristine and to experimental topical use of retinoids [3].

After successful treatment of KS, esthetically disturbing postinflammatory hyperpigmentation often remains visible for a long time, which should not be confused with active KS.

8 Follow-up / surveillance

8.2 Follow-up

Since KS is prone to recurrence, regular surveillance must be performed.

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15 Authors' Affiliations

Dr. med. Franz A. Mosthaf
Gemeinschaftspraxis für
Hämatologie, Onkologie und Infektiologie
Zentrum für ambulante Onkologie
Kriegsstr. 236
76135 Karlsruhe
mosthaf@onkologie-ka.de

Prof. Dr. med. Stefan Esser
Universitätsklinikum Essen
Klinik für Dermatologie und Venerologie
Hufelandstr. 55
45122 Essen
stefan.esser@uk-essen.de

16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Mosthaf, Franz A.	Selbständig!	**Yes** 1 x advisory board für Janssen im Jahr 2022	**No**	**No**	**Yes** € 994.- 23.12.2022	**No**	**No**	**No**
Esser, Stefan	Universitätsklinikum Essen	**Yes** Ad Boards: Gilead, GSK, MSD, Janssen, ViiV	**No**	**No**	**Yes** Gilead, MSD, Janssen, ViiV	**Yes** Gilead, MSD, Janssen, ViiV	**Yes** Gilead, Janssen	**Yes** Gilead, Janssen

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[1] *- Current employer, relevant previous employers in the last 3 years (institution/location).*

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