no patient handout*

Non-AIDS Kaposi sarcoma - Skin

Synopsis

Kaposi sarcoma (KS) is a malignant neoplasm of lymphatic endothelial cell origin that occurs in several forms: **AIDS-associated**(discussed separately) and non-AIDS-related, including classic KS, endemic KS, and iatrogenically-induced KS. All 4 types can be linked to coinfection with **human herpesvirus type 8** (HHV-8).

Classic (traditional) KS is seen almost exclusively in people of Mediterranean and Ashkenazi Jewish descent. Older literature described classic KS occurring more often in males, with a male-to-female ratio of approximately 12:1. However, more recent studies suggest that the sex gap may not be so significant. Age of onset is typically between 50 and 70 years. Classic Kaposi sarcoma most commonly runs an indolent course for 10-15 years or more with slow enlargement of tumors and the gradual development of additional lesions. After many years, systemic lesions can develop along the gastrointestinal tract, in lymph nodes, and in other organs. These visceral tumors are usually asymptomatic. Up to one third of the patients with classic KS develop a second primary malignancy, most frequently non-Hodgkin lymphoma.

There is an aggressive endemic form in equatorial black Africans that is also unrelated to AIDS. Areas of highest prevalence include Uganda, the Congo Republic, Zambia, and Congo (Brazzaville). Systemic lesions are particularly prevalent in this form. The male-to-female ratio is nearly equal among children but increases with age.

Iatrogenic KS is the result of long-term systemic immunosuppression and is common in transplant recipients, especially renal. It may resolve when immunosuppressive medications are discontinued.

Codes

ICD10CM:
C46.0 – Kaposi's sarcoma of skin

SNOMEDCT:
109386008 – Kaposi's sarcoma of skin

Look For

Red, purple, or bluish black patches that slowly progress into rubbery plaques. Late lesions may appear verrucous. The violaceous hue may be less conspicuous on darker skin. The disease is often limited to the lower extremities, especially involving the ankles and feet. Venous stasis and lymphedema of the involved lower extremity are frequently seen. Oral and other mucosal tumors may occur.

Diagnostic Pearls

Lesions start distally, usually on the feet. Frequently, they are not recognized by patients and require removal of shoes and socks for the physician to consider this diagnosis.

Differential Diagnosis & Pitfalls

- **Angiosarcoma** – Usually occurs on the head and neck.
- Hemangioma
- **Prurigo nodularis**
- Hypertrophic **lichen planus**
- **Dermatofibroma** or **dermatofibrosarcoma protuberans**
- **Sarcoidosis**
- **Cat-scratch fever** – Has a similar vascular proliferation clinically (**bacillary angiomatosis**).
- Single lesions with rapid onset are consistent with a **lobular capillary hemangioma** (pyogenic granuloma).
- **Vasculitis**
- **Angiokeratoma**
- **Lichen simplex chronicus**
- **Metastatic carcinoma** or **melanoma**
- **Pigmented basal cell carcinoma**
- **Blue rubber bleb nevus syndrome**
- **Tufted angioma**
- **Cavernous hemangioma**
- **Arteriovenous malformation**
- **Lymphoma**
- **Leukemia cutis**
- Early KS may resemble a large junctional nevus or **port-wine stain**.

Best Tests

Skin biopsy is diagnostic. Consider HIV testing if the patient's HIV status is unknown.

Additional studies may be warranted to ascertain the extent of disease, including but not limited to CT scans, plain films, CBC, and fecal occult blood testing.

Histopathology Findings:
Common features

- Vascular proliferation in the dermis composed of varying proportions of neoplastic blood vessels and spindle cells
- Patch stage characterized by scarce discrete blood vessels with few or no spindle cells
- Plaque and nodular stage characterized by increased proportion of spindle cells surrounding neoplastic blood vessels
- Neoplastic vessels are poorly-defined, irregular (slit-like), thin walled, and lined by a single layer of thin, barely visible endothelial cells
- Neoplastic vessels are arrayed horizontally between collagen fibers and surround adnexa or preexisting vessels ("promontory sign")
- Spindle cells have eosinophilic cytoplasm and tapered hyperchromatic nuclei with variable pleomorphism
- Extravasated red blood cells and siderophages
- Perivascular inflammatory cell infiltrate composed of lymphocytes and plasma cells
- Immunostain: HHV8 positive nuclear staining

Occasional features

- Extension into the subcutis
- Endothelial cells may be plump (particularly in the plaque stage)
- Some normal mitotic figures
- Eosinophilic globules (signifying degenerated erythrocytes) present within or outside neoplastic spindle cells

Management Pearls

The treatment of KS is considered largely palliative. In elderly patients or those with multiple comorbidities and limited disease, the risks and benefits of pursuing aggressive treatment should be weighed carefully.

The treatment of advanced KS often necessitates a multidisciplinary approach. Medical or radiation oncologists may be needed to administer systemic chemotherapy or radiation therapy, respectively.

Therapy

Solitary lesions:
Cryosurgery (2 freeze-thaw cycles) every 3 weeks.

Radiation therapy, such as electron beam, can control tumors. Disease recurrence in adjacent untreated skin may be controlled when extended field radiation is used instead.

Panretin gel (alitretinoin 0.1%) applied to the lesion(s) every 12 hours. Note: This is a very expensive medication.

Intralesional vinblastine (0.1 mg).

Small superficial lesions can be excised individually but can recur locally. Multiple excisions over many years can yield good results with minimal invasive therapy.

Widespread skin disease:
Radiation therapy can be effective in controlling widespread disease. The type of radiation (ie, photon vs electron) and fields used must be tailored to suit the distribution of the lesions in the individual patient.

Chemotherapy is occasionally used. Some commonly employed regimens include weekly intravenous vinblastine (4-6 mg) or vinblastine alternating with vincristine (2 mg IV) on a weekly basis. Combination regimens include doxorubicin, bleomycin, and vincristine.

Reduction or cessation of immunosuppressive medications in patients with iatrogenic KS may be all that is necessary in the way of treatment. Attempt this first before moving on to other forms of therapy.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations

Medication	Citations
ACE inhibitor	1
adalimumab	1
Alkylating agent	2
Calcineurin inhibitor	2
Corticosteroid	4
cyclophosphamide	1
cyclosporine	2
infliximab	1
leflunomide	1
lisinopril	1
mycophenolate mofetil	1
prednisone	3
rituximab	1

Medication	Citations
temozolomide	1
triamcinolone	1

AIDS-associated Kaposi sarcoma

Synopsis

Kaposi sarcoma (KS) is a malignancy of vascular endothelial cells that occurs in several forms: classic KS, endemic KS, iatrogenically-induced KS, and human immunodeficiency virus (HIV)-associated KS. All 4 types can be linked to co-infection with **human herpesvirus type 8** (HHV-8), and the cutaneous lesions are morphologically and histologically indistinguishable among the types. KS may be a reactive process rather than a true neoplasm because it does not produce conventional metastases but spreads in a multifocal way.

The outbreak of KS among young, previously healthy men who have sex with men (MSM) heralded the recognition of **AIDS** in 1981. AIDS-associated KS is the most common neoplasm in HIV-seropositive patients. It is an AIDS-defining illness. This form of KS disproportionately affects MSM, African Americans (regardless of sexual orientation), and heterosexual African individuals. KS lesions have been reported in up to 35% of AIDS patients and are seen more commonly in those with CD4 counts less than 150-200 cells/mm^3.

Patients with AIDS-associated KS often have multifocal cutaneous disease. Around 20% of patients will have concomitant visceral involvement, which places these patients at risk for hemorrhage from gastrointestinal lesions, cardiac tamponade, and pulmonary obstruction. Additionally, AIDS-associated KS is more likely than classic KS to display a rapidly progressive course.

Spindle cells of endothelial origin are the predominant cell affected. In the latent phase, HHV-8 antigens promote cell proliferation by inactivating the *RB* gene, which leads to transcription of S-phase genes and blocks apoptosis via p53 and $p27^{Kip1}$ suppression. In the lytic phase, when tumour formation is noted, thousands of virion particles are assembled resulting in cell lysis. HHV-8 requires additional co-factors for the development of KS. HIV co-infection acts as a stimulant for HHV-8 viral lytic expression and via its suppression of the immune system.

The introduction of highly active antiretroviral therapy (HAART) dramatically decreased the incidence, morbidity, and mortality of AIDS-associated KS.

For discussion of classic, endemic, and iatrogenic forms, see **Non-AIDS Kaposi sarcoma**.

Codes

ICD10CM:
C46.0 – Kaposi's sarcoma of skin

SNOMEDCT:
420524008 – Kaposi's sarcoma associated with AIDS

Look For

Deep red, brown, or purple patches, plaques, or nodules that may occur anywhere on the body with a predilection for the face, posterior neck, earlobes, nose, and oral cavity (hard palate). Koebnerization (lesions occurring in areas of trauma) is occasionally seen. Often, lesions will have a linear morphology following skin tension lines. Acral lesions may become hyperkeratotic with psoriasiform scale or a verrucous appearance.

Diagnostic Pearls

Whereas classic KS favors the lower extremities, AIDS-associated KS lesions have multiple locations.

Patch stage KS may have an ecchymotic appearance.

Lymphedema of affected sites is frequently seen.

The presence of intraoral involvement should prompt a search for underlying gastrointestinal involvement.

Differential Diagnosis & Pitfalls

- **Bacillary angiomatosis**
- **Lobular capillary hemangioma** (pyogenic granuloma)
- **Vasculitis**
- **Dermatofibroma**
- **Cherry hemangioma**
- **Angiokeratoma**
- **Lichen simplex chronicus**
- **Prurigo nodularis**
- **Metastatic carcinoma** or **melanoma**

- **Pigmented basal cell carcinoma**
- **Blue rubber bleb nevus syndrome**
- **Tufted angioma**
- **Cavernous hemangioma**
- **Arteriovenous malformation**
- **Lymphoma**
- **Leukemia cutis**
- **Angiosarcoma**
- Early KS may resemble a large junctional nevus, a **port-wine stain**, or an ecchymosis.

Best Tests

Skin biopsy is diagnostic. Consider HIV testing if the patient's HIV status is unknown.

Additional studies may be warranted to ascertain the extent of disease, including, but not limited to, CT scans, plain films, CBC, and fecal occult blood testing.

Histopathology Findings:
Common features

- Vascular proliferation in the dermis composed of varying proportions of neoplastic blood vessels and spindle cells
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Management Pearls

In AIDS-associated KS, an infectious disease / HIV specialist should be involved to direct the treatment of the underlying HIV and other concomitant opportunistic infections. An oncologist may co-manage AIDS-associated KS.

Treatment of AIDS-associated KS with antiretroviral therapy (ART) has resulted in complete resolution of lesions in some due to the suppression of HIV replication with reconstitution of the immune response, the decrease in angiogenic Tat protein, and a decrease in cytokine production responsible for release of angiogenic factors.

Initiation of ART may lead to the development of immune reconstitution inflammatory syndrome and patients may present for the first time with lesions of KS, or those with pre-existing KS lesions may present with exacerbation or progression of their lesions. This is referred to as KS-IRIS, and the incidence has been reported to be between 6%-12%.

Therapy

The following modalities have been employed over and above combination ART:

Solitary Lesions

- Cryosurgery (2 freeze-thaw cycles) every 3 weeks. There is increased risk of post-inflammatory dyschromia in darker skin phototypes.
- Radiation therapy, such as electron beam, can control these exquisitely radiosensitive tumors. Disease recurrence in adjacent untreated skin may be controlled when extended field radiation is used instead.
- Excisional or laser surgery with risk of local recurrence.
- Topical alitretinoin 0.1% applied to the lesion(s) twice daily. Topical imiquimod 5% cream daily may also be tried.

- Intralesional bleomycin (1.5 mg), intralesional interferon-alpha (3-5 million units 3 times per week), or intralesional vinblastine (0.1 mg).

Widespread Skin Disease

- Radiation therapy can be effective in controlling widespread disease. The type of radiation (ie, photon versus electron) and fields used should be tailored to the distribution of the lesions in the individual patient.

- Chemotherapy is occasionally used. Some commonly employed regimens include weekly IV vinblastine (4-6 mg) or vinblastine alternating with vincristine (2 mg IV) on a weekly basis. Combination regimens include doxorubicin, bleomycin, and vincristine. Etoposide has been used successfully and has the added benefit of being able to be administered orally.

Pediatric Patient Considerations

- Vincristine with bleomycin has been used successfully in children. Oral etoposide has been used with equal efficacy and better tolerance than the vincristine-bleomycin combination.

New Therapies Under Investigation

- Ongoing clinical studies are presently being conducted to assess targeted therapies that intercept pathways active in KS development. These include mTOR inhibition with rapamycin, anti-angiogenic therapy with VEGF inhibitors (eg, bevacizumab, sunitinib) that inhibits c-kit signaling, and sorafenib that targets VEGF and PDGFR.

- Kaposi sarcoma lesion formation is noted during the lytic phase of HHV-8 infection. Chloroquine has been shown to inhibit mTOR and p-38 MAPK pathways during the lytic phase cycle of HHV-8 in an in vitro study.