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內文：

Introduction

1. Kaposi sarcoma (KS) is multifocal angioproliferative disorder of vascular endothelium, primarily affecting mucocutaneous tissues with the potential to involve viscera.
2. Four clinical variants:
   - Classic
   - Endemic
   - Iatrogenic
   - epidemic
3. Classic KS
   - a rare and mild form of the disease first described by the Hungarian dermatologist Moritz Kaposi in the 19th century
   - The male-to-female ratio for classic KS is 17:1
   - Multiple purplish-red pigmented plaques on the skin of arms, legs, and trunk of men older than 50 years in the endemic areas.
4. Iatrogenic KS

- refers to the form associated with the use of steroids, immunosuppressive agents, and drugs with antitumor necrosis factor (TNF) activity in patients with autoimmune disorders, inflammatory conditions, or solid organ transplantation.
- 3:1 male predilection
- tends to affect liver transplant patients more often than recipients of kidney or heart allografts.

5. endemic KS (or African KS)

- variant of disease affecting human immunodeficiency virus (HIV)-seronegative children and young adults in sub-Saharan Africa
- clinical course of endemic KS is variable and includes indolent skin disease, locally infiltrative lesions of extremities, and aggressive visceral involvement with potentially fatal sequela.
- Generalized lymphadenopathy is a common feature of endemic KS, and oral mucosa is infrequently affected.

6. Epidemic or acquired immunodeficiency syndrome (AIDS)-associated KS (AIDS-KS)
   - the most common variant and a more aggressive form
   - second-most frequent tumor affecting HIV patients worldwide
   - in the western hemisphere, HIV-seropositive male homosexuals are 5 to 10 times more at risk for KS compared with other groups with high-risk behaviors.
   - contrast with Africa, where AIDS-KS affects younger age groups and both genders, albeit unequally.

- more likely to occur in the context of advanced immunosuppression
- Epidemic KS often affects mucocutaneous tissues as multifocal plaques, patches, and nodules with a predilection for the face and lower extremities (Figs. 1 and 2)

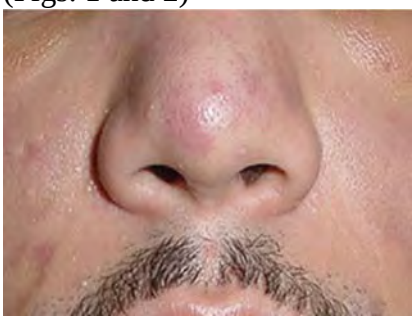

Fig. 1. Clinical presentation of an irregular pink patch at the tip of the nose of an HIV-positive male.

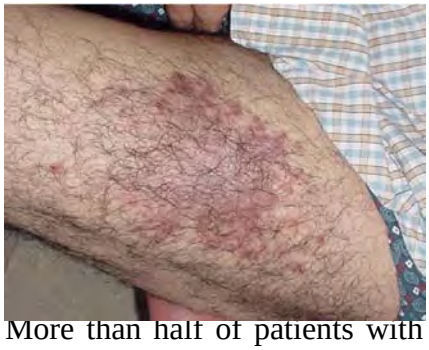

Fig. 2. Clinical presentation of an irregular light purple patch on the upper thigh of an HIV-positive male.

- More than half of patients with AIDS-KS may have visceral involvement Manifestation of AIDSKS in the gastrointestinal tract may occur independent of skin disease and lead to abdominal pain, diarrhea, weight loss, bleeding, and vomiting when symptomatic
- Pulmonary KS, the second-most common site of extracutaneous KS, is a late and potentially fatal complication presenting with cough, dyspnea, and hemoptysis in symptomatic patients
- Lymphedema, a complication resulting from obstruction of lymphatics, frequently affects the lower extremities and periorbital region of HIV patients

MANIFESTATION OF KS IN THE ORAL CAVITY

1. All forms of KS may present in the oral cavity; however,oral lesions are more likely to occur with the epidemic variant of the disease.
2. The oral cavity is the first clinical site of disease in 22% of patients with KS, and up to 71% of HIV patients may develop oral KS concurrent with cutaneous and visceral involvement.
3. most frequently affected oral sites include hard palate, gingival, and dorsal tongue
4. Oral KS may present as solitary, mutifocal, or multicentric macules, plaques, or nodules of different sizes, varying in color from deep red to bluish-purple

ROLE OF KSHV IN KS PATHOGENESIS

1. involves infection with human herpes virus type 8 (HHV-8), also known as Kaposi sarcoma–associated herpes virus (KSHV).
2. KSHV induces angiogenic and inflammatory cytokines, as well as gene products implicated in angiogenesis, may suggest a direct role for this virus in KS pathogenesis
3. Although necessary, KSHV may not be sufficient for initiation and

progression of KS.KSHV may be an essential but insufficient cofactor in KS pathogenesis.

4. In men coinfected with both HIV and KSHV, the KS hazards appear to increase by 60% for each year of infection with HIV and KS pathogenesis probably involves a synergistic action between these viruses.

KSHV SEROPREVALENCE AND MODE OF TRANSMISSION

1. KSHV has been detected in a variety of body fluids and potential routes of transmission include
   - vertical, horizontal through sex or oral shedding,
   - blood transfusion, and injection drug use
   - solid organ or BM transplantation
2. In regions where KSHV infection is endemic, infection is probably acquired in childhood from seropositive family members
3. In view of both spread of the HIV epidemic in Africa and poor access to highly active antiretroviral therapy (HAART), infected patients often develop rapidly progressive KS with life expectancy of fewer than 6 months.
4. In a cohort of HIV-seronegative males from Brazil, KSHV seroprevalence was higher among men who have sex with men (MSM) compared with males with an intravenous drug use habit, suggesting a sexual route for KSHV transmission.
5. Higher copy numbers of KSHV in saliva compared with semen have been found in patients with and without KS and independent of HIV status. It is possible that oropharyngeal epithelial cells harbor KSHV and facilitate its replication and shedding into saliva, contributing to viral transmission.

KS HISTOLOGY AND DIAGNOSIS

1. Differential diagnosis of clinical mucocutaneous lesions includes nevi, pyogenic granuloma, bacillary angiomatosis, hemangioma, angiosarcoma, and, when affecting bone-bearing oral tissues, also melanoma, leukemia, and lymphoma, as well as inflammatory or fibrotic gingival enlargements, necessitating histopathological tissue evaluation for definitive diagnosis.
2. Microscopic features of KS : abundance of proliferating mononuclear inflammatory and spindle cells, ill-defined vascular channels, hemorrhage, and edema
3. Initial workup for staging AIDS-KS involves a complete physical examination that includes evaluation of skin, oral cavity, and rectum, as well as a chest x-ray. When pulmonary or gastrointestinal disease is suspected, lesions may be visualized by bronchoscopy or endoscopy, respectively.

PATHOGENESIS OF KS

1. Lesions of KS are composed of a heterogeneous population of cells expressing a variety of antigenic profiles. For example, the endothelial cells of KS express both lymphatic and vascular immunophenotypes.
2. The current opinion suggests that infection of endothelial cell precursors by KSHV may lead to a cascade of intracellular events conducive to a hyperinflammatory state, angiogenesis, and lymphatic differentiation.
3. The pathogenesis of lymphedema in AIDS-KS may involve cytokine-driven local inflammation, KSHV-induced proliferation of lymphatic endothelial cells, obstruction of lymphatic channels, and enlargement of affected lymph nodes.

MANAGEMENT STRATEGIES

1. Selection of therapeutic interventions for KS depends on
   - the location and variant of KS

- the rate of progression and distribution of lesions
- the presence, absence, or severity of symptoms
- the efficacy and potential side effects of therapy
- the presence or absence of HIV infection and comorbidities
- the degree of host immune competence
- the prognosis and preference of the patient.

2. Therapy for KS aims to palliate symptoms, reduce tumor-associated edema, and improve esthetics and function.
3. Therapeutic approaches for classic KS range from no treatment to surgical excision, local interventions, and radiotherapy.
4. Management of iatrogenic KS often involves reduction or elimination of immunosuppressive therapy with or without local measures.
5. Endemic KS is frequently responsive to systemic chemotherapy.
6. Management of epidemic KS, in contrast, is not aimed at a cure but palliation and control of KS progression with HAART is considered an essential component of this process.

AIDS-KS AND HAART

1. There is evidence that epidemic KS often regresses with HAART and that HIV patients undergoing antiretroviral therapy have a less severe form of the disease compared with those naive to HAART at the time of KS diagnosis.
2. The current prognostic indicators for staging of AIDS-KS, proposed by Nasti et al., include tumor extension (T) and HIV-related systemic illness (S) resulting in good and poor survival risk categories depending on the combination of prognostic markers (Table I).

Table I. Post-HAART prognostic criteria in staging epidemic Kaposi sarcoma

Prognostic indicators[a]	*Definition*[b]
Tumor extension (T)	T_0 = restriction of lesions to skin and/or lymph nodes and/or minimal oral disease[c] T_1 = presence of tumor associated edema or ulceration, extensive oral disease, or visceral involvement
Systemic disease (S)	S_0 = no history of opportunistic infections, "B" symptoms,[d] Karnofsky Performance Status ≥70 S1 = history of opportunistic infections, "B" symptoms,[d] other HIV-related illnesses, Karnofsky Performance Status <70

Based on references 1, 34, 42, 121, 122.
[a and b]Initially described by ACTG Oncology Committee for staging AIDS-KS.
[c]Non-nodular solitary Kaposi restricted to palate.
[d]Unexplained fever, night sweats, >10% involuntary weight loss or diarrhea >2 weeks.

3. In the post-HAART study by Nasti et al.,121 treated HIV-positive patients with the combination of poor tumor stage (e.g., tumor-associated edema) and constitutional symptoms (T1S1) were found to have an unfavorable prognosis with a 3-year survival rate of 53%.
4. In contrast, HIV patients on HAART with none or only 1 prognostic criteria (T0S0, T0S1, T1S0) were found to have a good prognosis with 3-year survival

rates of 88%, 80%, and 81%, respectively.

5. HAART alone is not sufficient for advanced epidemic KS with poor prognostic index (T1S1), which requires additional interventions. When tolerable, AIDS-KS with unfavorable prognosis (e.g., pulmonary involvement or rapidly progressive disease) is best managed with a combination of HAART and systemic chemotherapy.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME—ASSOCIATED KS

1. Some HIV-infected patients are at risk of developing KS within a few weeks of HAART initiation. This phenomenon typically affects younger individuals who are profoundly immunosuppressed (CD4＜100 cells/mm3) at the time of HAART introduction.
2. This paradoxical exacerbation of opportunistic infections, such as KS, despite immunologic recovery and favorable virological response with HAART is known as immune reconstitution inflammatory syndrome (IRIS).
3. Although acute IRIS occurs in response to a subclinical infection within the first 3 months of HAART initiation, delayed IRIS often develops against antigenic components of dead pathogens anytime after the first 3 months of therapy.
4. The 5 drugs currently approved by the Food and Drug Administration (FDA) for treatment of HIV-KS include
   - 0.1% alitretinoin gel for topical therapy
   - daunorubicin citrate liposome (DNX)
   - pegylated li-posomal doxorubicin (PLD)
   - taxane paclitaxel
   - interferon alpha-2b for systemic therapy.
5. Tables II and III, respectively, provide an overview of the management strategies and the spectrum of therapeutic modalities for epidemic Kaposi sarcoma.

Table II. Potential management strategies for epidemic Kaposi sarcoma based on disease severity

Severity of AIDS-KS	*Management approach*
• T_0S_0 (focal disease in the absence of systemic illness)[1,34]	
• T_0S_1 (early but mildly symptomatic KS, e.g., minimal cutaneous disease)[1,34]	HAART ± local therapy[1,34]
• T_1S_0 (slowly progressive AIDS-KS)[34]	HAART[34]
• Extensive disfiguring skin lesions[1]	
• Widespread, symptomatic cutaneous AIDS-KS + edema[1]	
• Rapidly progressive AIDS-KS[1,34]	
• Symptomatic visceral involvement[1,34]	
• Obstructive or painful oropharyngeal AIDS-KS[1]	
• Inadequate response to HAART alone[1]	
• IRIS-associated KS[34]	

Based on reference 34. *AIDS,* acquired immunodeficiency syndrome; *HAART,* highly active antiretroviral therapy; *IRIS,* immune reconstitution inflammatory syndrome; *KS,* Kaposi sarcoma.

Table III. Spectrum of therapeutic modalities for epidemic Kaposi sarcoma

Local/regional therapy
- surgical excision[11,15,137]
- cryotherapy[148]
- sclerotherapy[149,150]
- intralesional vinca-alkaloids,[137,144,145,149] bleomycin,[146] interferon-alpha[147]
- topical 0.1% alitretinoin,[151,152,*] imiquimod 5% cream[153]
- radiotherapy[138-141]
- laser therapy[142,143]

Systemic therapy

HAART
- NNRT-based therapy[130]
- PI-based therapy[130,131]

Chemotherapy
- Liposomal anthracyclins[154,155,*]
- Paclitaxel[156,*]
- Oral etoposide[157-159,*]
- Combination agent ABV[154,155,160] or ABVb[159]
- Single agent vincristine,[161] vinblastine,[162] vinorebline,[163] bleomycin[164]

Immune modulators
- Interferon-alpha 2b[165-167,*]

Experimental & targeted therapies
- Antiherpes therapy[168-170]
- Angiogenic inhibitors (e.g., thalidomide)[171,172]
- VEGF inhibitors[173]
- Tyrosine kinase inhibitors[174]
- Matrix metalloproteinases[175]

ABV, doxorubicin, bleomycin, vincristine; *ABVb*, doxorubicin, bleomycin, vinblastine; *HAART*, highly active antiretroviral therapy; *NNRT*, non-nucleoside reverse transcriptase; *PI*, protease inhibitor; *VEGF*, vascular endothelial growth factor.
*Drugs approved by the US Food and Drug Administration for epidemic Kaposi sarcoma.

LOCAL THERAPY

1. introduction
   - Local therapy is safe, easy to administer, and efficacious for limited, asymptomatic mucocutaneous lesionsof AIDS-KS
   - It may also be considered when HAART is unavailable, response to HAART is less than optimal, or as a palliative measure in patients with rapidly progressive mucocutaneous lesions causing pain, esthetic concerns, or interference with oral function.
   - In spite of these benefits, the local approach is often costly and frequently unsuccessful in controlling the onset of new lesions.
2. Radiotherapy
   - Radiotherapy is highly effective for management of local or regional KS causing pain, bleeding, or edema and remission rates in excess of more than 90% for AIDS-KS have been documented
   - Potential drawbacks of radiotherapy include risk of radiodermatitis with repeated cutaneous exposure, disease relapse because of radiationinduced fibrosis, and hyperpigmentation.
   - Adverse effects, such as severe mucositis, hyposalivation, and dysguesia have been reported

3. Surgical excision
   - The focal, superficial mucocutaneous KS is amenable to surgical excision.
   - Potential drawbacks include functional impairment with repeat procedures in anatomical areas where tissue is sparse, as well as local recurrence of KS.
   - In addition,oral KS is often diffuse or multifocal and not suitable for surgical excision.
4. Intralesional injection
   - Intralesional injection with vinca alkaloids, such as vincristine and vinblastine, known to disrupt microtubular function, has been efficacious for local treatment of mucocutaneous lesions of classic and epidemic KS.
   - The procedure is painful, there is potential for necrosis if healthy tissue is injected, and therapeutic effects last about 4 months.
   - Cryotherapy with liquid nitrogen for focal skin lesions of AIDS-KS have been tried, yielding full resolution in 80% of cases, although the procedure may be associated with local blistering and pain.

SYSTEMIC CHEMOTHERAPY

1. Systemic chemotherapy is generally indicated for advanced disease with poor prognostic index.
2. first-line systemic
   - current first-line systemic therapy for advanced, progressive AIDS-KS includes liposomal anthracyclines, including PLD and DNX.
   - In patients with moderate to severe AIDS-KS, the addition of PLD to HAART led to a significantly better response rate (76%) compared with HAART alone (20%).
   - Main adverse affects include myelosuppression and opportunistic infections.
   - Toxicity relevant to DNX includes stomatitis and infusion reactions.
3. second-line systemic
   - Approved by the FDA for AIDS-KS in patients refractory to or intolerant of liposomal anthracycline, is paclitaxel.
   - Paclitaxel polymerizes microtubules and interferes with cell division. The response rate of advanced AIDS-KS to paclitaxel in different studies varies, but is reported as high as 71%.
   - The intravenous mode of administration and the potential for bone marrow suppression, peripheral neuropathy, renal dysfunction, alopecia, and arthralgia renders paclitaxel a less favorable agent than liposomal anthracyclines in the management of widespread KS.
4. Cytotoxic regimens
   - Cytotoxic regimens with single or multiple chemotherapeutic agents for AIDS-KS may be considered when first- and second-line therapies (liposomal anthracycline and paclitaxel) are unavailable or failed to resolve the disease.
   - Vincristine: Single-agent vincristine is efficacious for AIDS-KS, has a favorable hematological profile, and is generally safe for anemic and neutropenic patients.1 The potential risk for neurotoxicity.
   - Vinblastine: Systemic vinblastine alone was found effective in 25% of AIDS-KS cases treated, providing remission for nearly 4 months. Although less neurotoxic than vincristine, the risk of myelosuppression is a concern with systemic administration of vinblastine.

PATHOGENESIS-BASED THERAPEUTIC APPROACHES

1. To improve efficacy and overcome chemotherapyassociated toxicity, new

therapeutic approaches have focused on direct control of KSHV for prevention and treatment of KS.

2. Anti-herpes drugs ganciclovir and foscarnet were found to reduce the risk of KS by up to 62% among HIV-positive subjects.
3. Although limited efficacy does not support the use of anti-herpes drugs alone,1 the combination of anti-herpes medications with HAART offers the promise to diminish replication of both viruses, prevent new lesions, and help regress lesions already present.

ROLE OF THE ORAL HEALTH CARE PROVIDER

1. Oral health care practitioners should be familiar with orofacial manifestations of KS, contribute to prevention of KS by educating patients about risk factors, and question those engaged in risk behaviors about the presence of mucocutaneous lesions.
2. Therefore, oral lesions clinically suggestive of KS should be biopsied and patients with biopsy-proven KS should be tested for HIV.

(1) Close communication between an oral health care provider and the patient's infectious disease specialist facilitates a mutual understanding of the extent of KS spread, severity of symptoms, available therapeutic strategies, and potential adverse effects of therapy.

題號	題目
1	Which type of Kaposi's sarcoma is related to use of immunosuppressive drug? (A) Classic (B) Endemic (C) Iatrogenic (D) Epidemic
答案(C)	出處：Oral and Maxillofacial Pathology 3rd edition, Ch.12 soft tissue tumors, p.558
題號	題目
2	Which virus below appears to involved in the pathogenesis of Kaposi's sarcoma?
	(A) varicella-zoster virus (VZV or HHV-3) (B) Epstein-Barr virus (EBV or HHV-4) (C) Cytomegalovirus (CMV or HHV-5) (D) Human herpevirus 8 (HHV-8)
答案(B)	出處：Oral and Maxillofacial Pathology 3rd edition, Ch.7 viral infections, p.240