Review Article

Recapitulation of acquired immuno deficiency syndrome associated Kaposi's sarcoma

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Abstract

Acquired immuno deficiency syndrome (AIDS) associated Kaposi's sarcoma (KS) is one of the clinical forms of KS. KS is caused by human herpes viruses 8 or KS associated herpes virus (KSHV). In India, till now, only 16 cases of AIDS associated KS was reported. Of all the clinical forms of KS, AIDS associated KS is distinct in many ways viz.; cutaneous manifestations commonly affects face and trunk rather than lower limbs, more mucosal lesions, rapidly progressive, and early systemic involvement. When human immunodeficiency virus (HIV) is co-infected with KSHV, in addition to the other pathogenic factors for the development of KS, HIV Tat protein promotes the proliferation of cytokine-activated endothelial cells and stimulates KS. Moreover, actions of HIV Tat lead to the aggressive course of KS in patients with AIDS, compared with the more confined behavior of KS in HIV-negative persons. Similarly, latency-associated nuclear antigen of KSHV would enhance HIV replication by activating the long terminal repeats of HIV-1 through its association with Tat. Effective antiretroviral treatment in AIDS associated KS results in reduction of the incidence of AIDS-related KS and regression of the existing lesions. Early diagnosis and treatment of AIDS associated KS would definitely increase the life span and quality of the patients.

Key words: AIDS, Herpes Virus, Kaposi's sarcoma associated virus

INTRODUCTION

Moritz Kaposi[1] first described Kaposi's sarcoma (KS) in 1872 as "idiopathic multiple pigmented sarcoma" in elderly patients. But it was Sternberg[2] who named this condition as KS in 1912. There are four clinical types of KS namely; (1) classical or sporadic, (2) endemic or African, (3) iatrogenic or immunosuppressed, and (4) acquired immuno deficiency syndrome (AIDS) associated or epidemic. Of these types, endemic and AIDS associated types are more aggressive. Nearly for 100 years, the etiology for KS was not confirmed and only in 1994, Chang *et al.*[3] described KS causing human herpes virus (KSHV) as the causative organism for KS. KSHV is responsible for all the clinical types of KS. The incidence of KS is directly proportional to the prevalence of KSHV in that geographical area. Before the human immunodeficiency virus (HIV) epidemic, KS prevalence was low and also it was less aggressive. HIV, in particular HIV Tat protein stimulates KSHV leading to a widespread infection in patients. In reciprocation, latency associated nuclear antigen (LANA) of KSHV enhances the HIV replication. KS is one of the AIDS-defining illnesses, and the diagnosis of AIDS made due to KS is ranging from 4.1% to 7.5%.[4] Fortunately, initiation

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of anti-retroviral therapy (ART) in AIDS associated KS at early stage shows a definite clinical and histological regression of KS, leading to increase the life span of the patients. This article elaborates about AIDS associated KS in detail.

KAPOSI'S SARCOMA CAUSING HUMAN HERPES VIRUS

It belongs to the eighth type of the pathogenic human herpes viruses 8 (HHV-8). KSHV, a lymphotropic herpes virus encodes a number of oncogenes involved in abnormal cell proliferation, antiapoptosis, angiogenesis, and cytokine activation.[5] After Epstein–Barr virus, KSHV is the second HHV that is linked to cancers. This oncogenic virus causes not only KS but also primary effusion lymphoma and multicentric Castleman disease. In addition to these, KSHV is also associated with hemophagocytic lymphohistiocytosis.[6] It is transmitted through sexual route and nonsexual routes such as deep kissing, organ transplantation, and needle sharing. Hence, sexual abstinence, monogamy, condom use, avoidance of intra venous drug use, and use of sterile needles and syringes are the best methods in avoiding the exposure to both KSHV and HIV. Healthy people acquiring this virus will remain asymptomatic while in people with HIV, immunosuppressive drugs, and other immunosuppressive conditions, it produces the tumor (KS). It has synergistic interactions with HIV in producing the KS.

EPIDEMIOLOGY

Before the emergence of HIV, KS was seen in central Africa, Mediterranean countries, and Middle East. It rarely occurred in other areas. The seroprevalence of HHV-8 varies significantly in geographical areas, with low to moderate infection rates in Western countries, Asia, and high (50%) in Sub-Saharan African countries.[7] In India, the incidence of AIDS associated KS is on the rise as more than 50% of the cases are reported from 2008 to 2010.[8] In India, till now, only 16 cases of AIDS associated KS was reported.[9] AIDS associated KS occurs commonly in homosexual males, bisexual men, and also in the female sexual partners of bisexual men. AIDS associated KS usually occurs in persons of 20–54 years. The morbidity in AIDS associated KS is mainly due to disfiguring cutaneous lesions, lymphedema, and systemic involvement; mainly gastrointestinal (GI) and pulmonary. The most common factor leading to mortality in AIDS associated KS patients is uncontrolled pulmonary hemorrhage.

PATHOGENESIS

Like all herpes viruses, the life cycle of KSHV has latent and lytic replication phases. Latency allows KSHV to escape from the host immune surveillance and facilitate the lifelong persistent infection. Since both latent and lytic replication phases are essential for the development of KS tumor, understanding the mechanisms of KSHV latency and reactivation helps us to elucidate KSHV-induced pathogenesis which in turn open up new avenues for novel treatments. Once KSHV enters the host, it triggers the innate immune responses such as interferons-alpha/beta (IFN-α/β) and interferon regulatory factors which in turn suppress the KSHV replication. This repressed KSHV enters the latency phase expressing only the latent genes including LANA-1, vCyclin, vFLIP, and miRNAs. Factors such as hypoxia, HIV infection, inflammatory cytokines, oxidative stress, and reactive oxygen species can induce replication transcriptional activator (RTA) expression by activating specific cellular pathways and transcriptional factors including MEK/ERK, JNK, p38, and Notch. RTA interacts with several host proteins such as XBP-1, and C/EBPα, as well as viral proteins such as MTA and kb-ZIP, resulting in the expression of viral lytic genes and activation of the entire viral lytic transcriptional proteins.[10] These viral lytic genes encode many oncogenes which induces tumor genesis in endothelial cell lineage resulting in KS [Figure 1].

SYNERGY BETWEEN KAPOSI'S SARCOMA ASSOCIATED HERPES VIRUS AND HUMAN IMMUNODEFICIENCY VIRUS

In the scenario of co-infection KSHV and HIV, HIV transactivating protein (Tat) protein,[11] and HIV-1 negative factor[12] interacts with KSHV viral interleukin and induces angiogenesis and tumorigenesis [Figure 2]. The Tat protein is responsible for aggressive course of KS in patients with AIDS,[13] when compared to the more indolent behavior of KS in HIV negative persons. Reciprocally, the LANA of KSHV activates long terminal repeats of HIV-1 through its association with Tat and enhances HIV replication.[14]

CLINICAL PRESENTATIONS OF ACQUIRED IMMUNE DEFICIENCY SYNDROME ASSOCIATED KAPOSI'S SARCOMA

AIDS associated or epidemic KS is the most common cause of tumor development among HIV infected

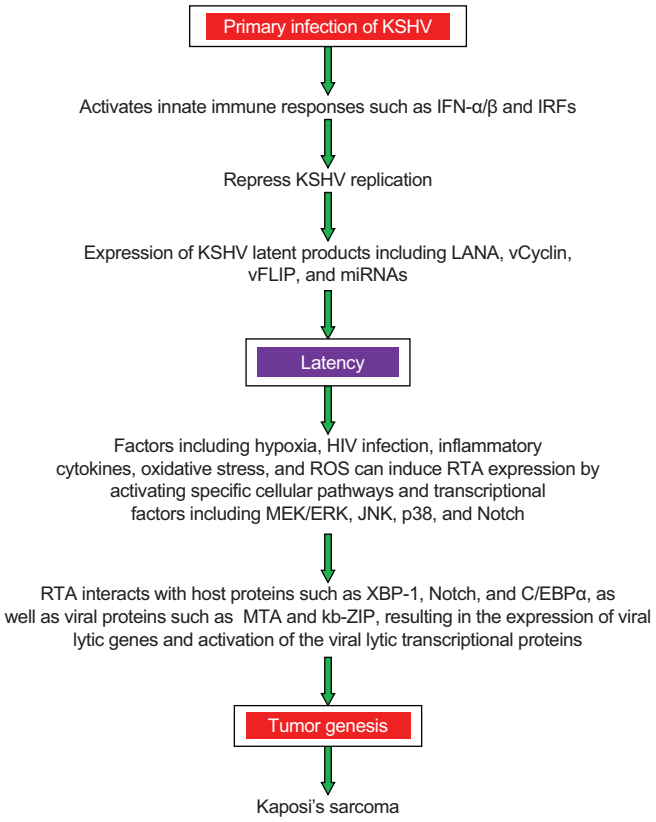

Figure 1: Pathogenesis of Kaposi's sarcoma. KSHV = Kaposi's sarcoma associated herpes virus; IFN-α/β = Interferons-alpha/beta; IRFs = Interferon regulatory factors; LANA = Latency-associated nuclear antigen; ROS = Reactive oxygen species; RTA = Replication transcriptional activator; HIV = Human immunodeficiency virus

patients in developed countries whereas in India, non-Hodgkin's lymphoma and cervical cancers are more common[15] than KS probably because of the low prevalence of KSHV. AIDS associated KS has a variable clinical course. It may affect skin, oral mucosa, lymph nodes, or visceral organs. Most patients present with skin disease. The cutaneous manifestations are characterized by brownish or violaceous macules, patches, plaques, and nodules extensively involving the trunk, face, limbs (unlike the classical KS where the skin lesions are seen in lower limbs). Skin lesions range in size from a few millimeters to large confluent areas. Few patients exhibit yellow to green "halo," (representing extravasated erythrocyte pigments) around the red or violaceous lesions. Pigmentation may persist even after the treatment. Similar lesions would also affect oral mucosa, commonly in gingiva, hard palate, oropharynx, alveolar mucosa, and the dorsum of the tongue. The oral cavity will be affected in up to 71% of patients with AIDS associated KS.[16,17] The extensive oral lesions are usually associated with facial edema. These oral lesions interfere with eating and speaking, cause tooth loss, or difficulty in breathing.

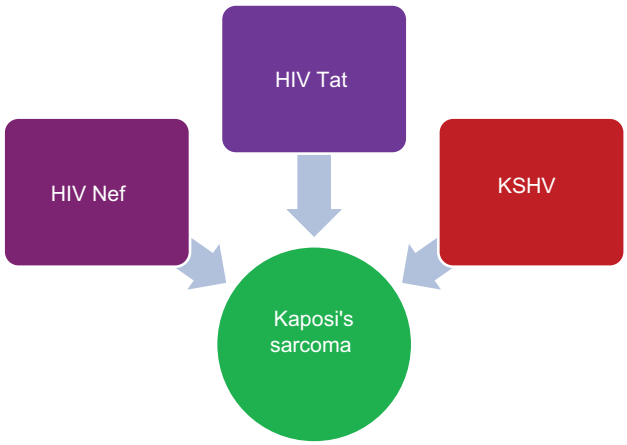

Figure 2: Synergy between Kaposi's sarcoma associated herpes virus and human immunodeficiency virus

Systemic illness is not uncommon; lungs and GI tract are frequently affected. Reports state that GI involvement is of 40% of patients with AIDS-associated KS at the time of initial KS diagnosis, and of 80% at autopsy. GI KS may occur without skin manifestations. KS may occur throughout the GI tract, and usually it is asymptomatic, some patients may experience pain, obstruction, or bleeding. KS may involve the lung parenchyma, bronchial tree, and pleural surfaces. Mostly, patients with pulmonary KS have advanced HIV disease. Physical presentations include shortness of breath, cough, wheezing, hemoptysis, and finally respiratory failure may occur. KS may involve many viscera including liver, spleen, heart, pericardium, bone, and bone marrow.

Lymphedema is a frequent sequele of AIDS-associated KS. It presents as nonpitting edema usually in the feet and legs, but also seen in groin, external genitalia, and the periorbital tissues. Edema is either due to the tumor involvement of dermal lymphatics or, because of the increased vascular permeability due to the factors secreted by the KS cells.

The impact of KS on quality of life is vacillating. Only few KS lesions are painful, particularly those on the soles of the feet. Edema of the extremities, genitalia, or peri-orbital tissues can cause difficulty in walking, urination, and vision, respectively. These lesions may be complicated by local infection or ulceration. Because of the disfiguring skin lesions, KS patients may have depression and anxiety. Oral or GI tract KS may result in nutritional deficiencies. Lung KS can lead to respiratory compromise. But early interventions in AIDS associated KS would avoid most of the above complications.

STAGING OF ACQUIRED IMMUNE DEFICIENCY SYNDROME ASSOCIATED KAPOSI SARCOMA

Till now, there is no consensus for any classification system in staging AIDS associated KS. But the most widely used system is AIDS Clinical Trials Group system,[18] which considers three factors for staging; extent of the tumor, status of the immune system, as measured by the number of CD4 cells present in the blood [Table 1]. The staging system would be helpful in the evaluating the prognosis of the patients.

INVESTIGATIONS

A punch biopsy of the skin lesions is diagnostic in AIDS associated KS to distinguish from other pigmented skin conditions such as bacillary angiomatosis, non-Hodgkin lymphoma, and cutaneous fungal or bacterial infections. The histological features vary depending on the clinical lesions, as it progresses from the patch to plaque to nodular phase.

Patch stage

It is the earliest phase in the evolution of cutaneous KS. It shows the signs of a subtle angiogenesis composed of newly formed slit-like vascular spaces, in the immediate vicinity of native dermal vessels and appendages. The protrusion of these native vascular structures into the lumens of newly formed ectatic neoplastic channels results in the characteristic "promontory sign."[19] The intervening dermis frequently reveals dissection of its collagen bundles by slit-like vascular spaces lined with a single layer of flattened endothelial cells, with a variable degree of erythrocyte extravasations. There is also a mild inflammatory cell infiltrate comprising lymphocytes and plasma cells.

Plaque stage

It is characterized by a diffuse dermal vascular infiltrate, with greater cellularity. The lesional cells tend to be more spindled and arranged in short, haphazard fascicles. Fascicles if cut in cross section reveal a sieve-like appearance. Mitotic figures are minimal and there is no significant nuclear atypia. Intra- and extra-cellular hyaline globules, representing erythrocytes are seen. The histological differential diagnosis is tufted angioma, targetoid hemosiderotic hemangioma, and acroangiodermatitis or pseudo KS.

Nodular stage

It demonstrates dermal expansion by a circumscribed, variable cellular proliferation of spindled cells arranged in fascicles. Erythrocytes are contained within slit-like channels between the individual spindled cells. Occasional mitotic figures are seen, the lesional cells are relatively monomorphic. Hyaline globules are more readily seen. In larger punch biopsy or excision biopsy specimens, the dermis away from the tumor nodule frequently reveal the changes associated with plaque stage KS, thus supporting the fact that patch, plaque and nodular stage lesions form part of a morphologic spectrum. Lesions that may be confused histologically with nodular KS include bacillary angiomatosis, fibrohistiocytic tumors, resolving dermal fasciitis, and several other spindle cell mesenchymal neoplasms.

Histological variants of Kaposi' sarcoma

Apart from the classical histological features of KS, there are other variants such as hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, and intravascular types.[20]

Regressing Kaposi sarcoma

Intervention with highly active ART may lead to complete regression of established AIDS associated KS lesions.[21] Clinical features of regression include reduction in lesion size, and numbers. Histologically, nodular lesions appear to be less cellular and are enveloped by a densely sclerotic stroma.[22] In few cases, the only significant abnormalities are

Table 1: Acquired immune deficiency syndrome Clinical Trials Group staging classification for Kaposi's sarcoma

Features	Good risk (0)	Poor risk (1)
Tumor	Confined to skin and or Lymph nodes and or Minimal oral disease[a]	Tumor associated edema or ulceration Extensive oral KS Gastro intestinal KS KS in other nonnodal viscera
Immune system	CD4 ≥200/μL	CD4 ≤200/μL
Systemic illness	No history of OI or thrush No "B" symptoms[b] Performance status ≥70 (Karnofsky)[c]	"B" symptoms present Performance status <70 Other HIV related illness (e.g., neurological disease, lymphoma)

aMinimal oral disease is nonnodular KS confined to the palate; b"B" symptoms are unexplained fever, night sweats, >10% involuntary weight, or diarrhea persisting for >12 weeks; cPatient is up and about most of the time and able to take care of him- or herself. KS=Kaposi's sarcoma; HIV=Human immunodeficiency virus; OI=Opportunistic infection

an increase in dermal capillary density around native dermal vessels and appendages, and an accompanying perivascular infiltrate of plasma cells. Partial or complete regression of KS lesions may show residual spindled cells around native vessels in the mid- and upper-dermis.[23]

Other than skin biopsy, nonspecific endothelial markers CD31 and CD34, and lymphatic endothelial marker D2–40 or podoplanin are useful in KS diagnosis.[24] The immunohistochemistry technique using the antibody anti-latent nuclear antigen-1 of the KSHV is reliable and cost-effective method in detecting the presence of the virus in the tumor cells and to differentiate KS from its histological simulators.[25]

Other investigations like chest radiography (may show diffuse reticulonodular infiltrates, pleural effusions, hilar lymphadenopathy, or an isolated pulmonary), esophago-gastro-duodenoscopy or colonoscopy is useful in identifying pulmonary and GI KS, respectively.

TREATMENT

Before the availability of ART, 90% of patients with AIDS associated KS had fatal end. Recent multivariate analyses of the AIDS Cohort Study revealed an 81% reduced risk of death for KS patients treated with ART.[26] Protease inhibitors (PI) and nonnucleoside reverse transcriptase inhibitors (NNRTI) based regimens were equally effective in AIDS associated KS.[27] Hence, the latest recommendation is triple nucleoside reverse transcriptase inhibitors or NNRTI-based therapy rather than PI-based therapy.[28] After the initiation of ART, KS may have a flare phenomenon, immune reactivation inflammatory syndrome.[29]

The factors that decide the choice of local versus systemic therapy for patients with AIDS-associated KS are cited in Table 2.

Table 2: Factors that determine local versus systemic therapy in acquired immune deficiency syndrome associated Kaposi's sarcoma

Local therapy	Systemic therapy
No skin lesions over the previous months	Rapidly progressive mucocutaneous disease (>10 new lesions in the preceding months)
Fewer than 10 skin lesions over the previous months	Symptomatic lymphedema
Patients with isolated, cosmetically disfiguring lesions	Symptomatic internal disease (pulmonary KS or any other internal KS)
Limited number of painful lesions	
Decreased tolerance to systemic therapy as in advanced HIV infection	

HIV=Human immunodeficiency virus; KS=Kaposi' sarcoma

LOCAL THERAPY

Radiation therapy

Radiation therapy, the most widely used one gives effective relief of cosmetically disturbing lesions or localized bulky symptomatic disease at any site.[30] Responses have been seen with dosing schedules ranging from single doses of 800 cGy to fractionated schemes with total doses exceeding 4000 cGy.

Intralesional chemotherapy

Typically, 0.1 ml of a dilute solution containing 0.2 mg/ml of vinblastine is injected into a lesion using a tuberculin syringe. Repeated injections may be necessary. Responses are partial, and recurrence in 4–6 months is common. The use of intralesional IFN-α (3–5 million units three times per week for 3–4 weeks) provides similar results. Injections are painful and associated with local inflammatory reaction.

Liquid nitrogen cryotherapy

One treatment consisted of two freeze-thaw cycles, with thaw times ranging from 11 to 60 s per cycle. A complete response was observed in 80% of treated KS lesions and lasted a minimum of 6 weeks following the completion of therapy. More than 50% cosmetic improvement of KS was observed. Hypopigmentation is the unwanted adverse effect resulting from the treatment.

Topical retinoids

Retinoids have been shown to inhibit KS cell growth by down regulating the interleukin-6 receptor expression.[31] The initial recommended dose of alitretinoin (9-cis-retinoic acid) 0.1% gel is to apply twice daily for 2 weeks, increasing up to four times daily as tolerated. The most common side effects are local erythema and irritation at the application site.

Systemic therapy

Currently available effective systemic therapies include IFN-α with or without antiretroviral agents and cytotoxic chemotherapy.

Interferon

IFN-α was the first drug specifically approved for the treatment of KS. It is of great interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties. When used as a single agent, IFN-α is effective at relatively high doses, i.e., 36 MU subcutaneously daily.[32] If IFN-α is combined with ART, it is effective even in 10 MU. The relatively slow onset of response seen with IFN-α

therapy makes this inappropriate for patients with advanced, rapidly progressive KS. The adverse effects of IFN-α is dose dependent. At daily doses of 1 MU, IFN-α results in little toxicity. On high doses, flu-like syndrome occurs. Prolonged administration of IFN-α, particularly at high doses (>20 MU subcutaneously daily), result in persistent fevers, anorexia, weight loss, and neuropsychiatric symptoms.

Cytotoxic chemotherapy

Chemotherapy result in fast resolution of KS-associated symptoms and thereby improve the quality of life. It could be either with single agents or combination chemotherapy. Single cytotoxic agents include liposomal doxorubicin, daunorubicin for first-line use, and paclitaxel or oral etoposide for second-line use. Liposome-encapsulated daunorubicin is given as 40 mg/m^2 intravenously or doxorubicin 10 mg/m^2 over 30–60 min every other week. Side effects were significantly less for patients treated with these liposome-encapsulated agents. Alopecia, neuropathy, and myelosuppression were minimal when compared to the combination therapy. Response rates range from 21% to 80% can be seen with these single cytotoxic drugs.[33] The effective combination therapy regimen is ABV (actinomycin D, bleomycin, and vincristine). Response rates for combination regimens vary from 28% to 88%.[34]

INVESTIGATIONAL THERAPY

Many different drugs are in trial to treat AIDS-related KS comprehensively. Thalidomide had 40% response rate in a study conducted by Little *et al*.[35] Uldrick *et al*. conducted a Phase II study with bevacizumab showing promising results.[36] Nasal formulation of glufanide disodium, an antiangiogenic dipeptide from thymic extract, has shown good response rates.[37] Because of its etiologic link to KSHV, foscarnet, and ganciclovir may be effective in few cases.[38] Rapamycin appears to be safe and induce tumor regression.[39] Antitumor activity was noted in the matrix metalloproteinase inhibitor, chemically modified tetracycline-3.[40]

CONCLUSION

The low number of reported cases in India could be either due to the real low prevalence of KSHV or lack of awareness in diagnosing KS. Hence, whenever we see pigmented skin lesions in a HIV patient, KS should be one among the differential diagnoses of the hyperpigmentary diseases. Proper documentation and reporting to the National Cancer Registry has to be improved. Like in Western countries, we should also start AIDS and Cancer Viral Program to elucidate more about the KSHV interactions with HIV.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sternbach G, Varon J. Moritz Kaposi: Idiopathic pigmented sarcoma of the skin. J Emerg Med 1995;13:671-4.
2. Campo-Trapero J, Del Romero-Guerrero J, Cano-Sánchez J, Rodríguez-Martín C, Martínez-González JM, Bascones-Martínez A. Relationship between oral Kaposi 's sarcoma and HAART: Contribution of two case reports. Med Oral Patol Oral Cir Bucal 2008;13:E709-13.
3. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, *et al*. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;266:1865-9.
4. Chung CY, Park SW, Myung E, Cho DK, Song YA, Park KJ, *et al*. AIDS-related gastrointestinal Kaposi sarcoma in Korea: A case report and review of the literature. Korean J Gastroenterol 2012;60:166-71.
5. Cathomas G. Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) as a tumour virus. Herpes 2003;10:72-7.
6. Grossman WJ, Radhi M, Schauer D, Gerday E, Grose C, Goldman FD. Development of hemophagocytic lymphohistiocytosis in triplets infected with HHV-8. Blood 2005;106:1203-6.
7. Zhang T, Shao X, Chen Y, Zhang T, Minhas V, Wood C, *et al*. Human herpesvirus 8 seroprevalence, China. Emerg Infect Dis 2012;18:150-2.
8. Joshi U, Ceena DE, Ongole R, Sumanth KN, Boaz K, Jeena Priy K, *et al*. AIDS related Kaposi's sarcoma presenting with palatal and eyelid nodule. J Assoc Physicians India 2012;60:50-3.
9. Agarwala MK, George R, Sudarsanam TD, Chacko RT, Thomas M, Nair S. Clinical course of disseminated Kaposi sarcoma in a HIV and hepatitis B co-infected heterosexual male. Indian Dermatol Online J 2015;6:280-3.
10. Ye F, Lei X, Gao SJ. Mechanisms of Kaposi's sarcoma-associated herpesvirus latency and reactivation. Adv Virol 2011;2011:193860.
11. Zhou F, Xue M, Qin D, Zhu X, Wang C, Zhu J, *et al*. HIV-1 Tat promotes Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6-induced angiogenesis and tumorigenesis by regulating PI3K/PTEN/AKT/GSK-3ß signaling pathway. PLoS One 2013;8:e53145.
12. Zhu X, Guo Y, Yao S, Yan Q, Xue M, Hao T, *et al*. Synergy between Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6 and HIV-1 Nef protein in promotion of angiogenesis and oncogenesis: Role of the AKT signaling pathway. Oncogene 2014;33:1986-96.
13. Caselli E, Galvan M, Cassai E, Caruso A, Sighinolfi L, Di Luca D. Human herpesvirus 8 enhances human immunodeficiency virus replication in acutely infected cells and induces reactivation in latently infected cells. Blood 2005;106:2790-7.
14. Hyun TS, Subramanian C, Cotter MA 2nd, Thomas RA, Robertson ES. Latency-associated nuclear antigen encoded by Kaposi's sarcoma-associated herpesvirus interacts with Tat and activates the long terminal repeat of human immunodeficiency virus type 1 in human cells. J Virol 2001;75:8761-71.
15. Venkatesh KK, Saghayam S, Devaleenal B, Poongulali S, Flanigan TP, Mayer KH, *et al*. Spectrum of malignancies among HIV-infected patients in South India. Indian J Cancer 2012;49:176-80.

16. Hille JJ, Webster-Cyriaque J, Palefski JM, Raab-Traub N. Mechanisms of expression of HHV8, EBV and HPV in selected HIV-associated oral lesions. Oral Dis 2002;8 Suppl 2:161-8.
17. Epstein JB, Cabay RJ, Glick M. Oral malignancies in HIV disease: Changes in disease presentation, increasing understanding of molecular pathogenesis, and current management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:571-8.
18. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: A proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol 1989;7:1201-7.
19. Grayson W, Pantanowitz L. Histological variants of cutaneous Kaposi sarcoma. Diagn Pathol 2008;3:31.
20. Sangüeza OP, Requena L, editors. Malignant neoplasms. Kaposi's sarcoma. In: Pathology of Vascular Skin Lesions. *Clinicopathologic* Correlations. New Jersey: Humana Press; 2003. p. 217-35.
21. Wit FW, Sol CJ, Renwick N, Roos MT, Pals ST, van Leeuwen R, *et al*. Regression of AIDS-related Kaposi's sarcoma associated with clearance of human herpesvirus-8 from peripheral blood mononuclear cells following initiation of antiretroviral therapy. AIDS 1998;12:218-9.
22. Eng W, Cockerell CJ. Histological features of kaposi sarcoma in a patient receiving highly active antiviral therapy. Am J Dermatopathol 2004;26:127-32.
23. Pantanowitz L, Dezube BJ, Pinkus GS, Tahan SR. Histological characterization of regression in acquired immunodeficiency syndrome-related Kaposi's sarcoma. J Cutan Pathol 2004;31:26-34.
24. Rosado FG, Itani DM, Coffin CM, Cates JM. Utility of immunohistochemical staining with FLI1, D2-40, CD31, and CD34 in the diagnosis of acquired immunodeficiency syndrome-related and non-acquired immunodeficiency syndrome-related Kaposi sarcoma. Arch Pathol Lab Med 2012;136:301-4.
25. Pereira PF, Cuzzi T, Galhardo MC. Immunohistochemical detection of the latent nuclear antigen-1 of the human herpesvirus type 8 to differentiate cutaneous epidemic Kaposi sarcoma and its histological simulators. An Bras Dermatol 2013;88:243-6.
26. Tam HK, Zhang ZF, Jacobson LP, Margolick JB, Chmiel JS, Rinaldo C, *et al*. Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma. Int J Cancer 2002;98:916-22.
27. Portsmouth S, Stebbing J, Gill J, Mandalia S, Bower M, Nelson M, *et al*. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. AIDS 2003;17:F17-22.
28. Martinez V, Caumes E, Gambotti L, Ittah H, Morini JP, Deleuze J, *et al*. Remission from Kaposi's sarcoma on HAART is associated with suppression of HIV replication and is independent of protease inhibitor therapy. Br J Cancer 2006;94:1000-6.
29. Connick E, Kane MA, White IE, Ryder J, Campbell TB. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma during potent antiretroviral therapy. Clin Infect Dis 2004;39:1852-5.
30. Piedbois P, Frikha H, Martin L, Levy E, Haddad E, Le Bourgeois JP. Radiotherapy in the management of epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys 1994;30:1207-11.
31. Guo WX, Gill PS, Antakly T. Inhibition of AIDS-Kaposi's sarcoma cell proliferation following retinoic acid receptor activation. Cancer Res 1995;55:823-9.
32. Volberding PA, Mitsuyasu RT, Golando JP, Spiegel RJ. Treatment of Kaposi's sarcoma with interferon alfa-2b (Intron A). Cancer 1987;59 3 Suppl: 620-5.
33. Lewis B, Abrams J, Ziegler J, *et al*. Single-agent or combination chemotherapy of Kaposi's sarcoma (KS) in acquired immunodeficiency syndrome (AIDS)(abstract). Proceedings of the American Society of Clinical Oncology 1983;2:59.
34. Gill PS, Rarick M, McCutchan JA, Slater L, Parker B, Muchmore E, *et al*. Systemic treatment of AIDS-related Kaposi's sarcoma: Results of a randomized trial. Am J Med 1991;90:427-33.
35. Little RF, Wyvill KM, Pluda JM, Welles L, Marshall V, Figg WD, *et al*. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol 2000;18:2593-602.
36. Uldrick TS, Wyvill KM, Kumar P, O'Mahony D, Bernstein W, Aleman K, *et al*. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol 2012;30:1476-83.
37. Cattelan AM, Trevenzoli M, Aversa SM. Recent advances in the treatment of AIDS-related Kaposi's sarcoma. Am J Clin Dermatol 2002;3:451-62.
38. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. AIDS 1996;10:1101-5.
39. Krown SE, Roy D, Lee JY, Dezube BJ, Reid EG, Venkataramanan R, *et al*. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: An AIDS Malignancy Consortium study. J Acquir Immune Defic Syndr 2012;59:447-54.
40. Cianfrocca M, Cooley TP, Lee JY, Rudek MA, Scadden DT, Ratner L, *et al*. Matrix metalloproteinase inhibitor COL-3 in the treatment of AIDS-related Kaposi's sarcoma: A phase I AIDS malignancy consortium study. J Clin Oncol 2002;20:153-9.

MCQ for Review Article "Recapitulation of acquired immuno deficiency syndrome associated Kaposi's sarcoma *ID: IJSTD_117/15*"

1. Kaposi's sarcoma associated herpes virus causes all of the following except

(a) Kaposi's sarcoma **(b) Primary effusion lymphoma**

(c) Burkitt's Lymphoma **(d) Castleman disease**

2. Activation of the KSHV lytic transcriptional proteins is mainly due to

(a) LANA-1 **(b) vCyclin**

(c) vFLIP **(d) Replication transcriptional activator**

3. The most common cause of tumor development among HIV infected patients in India is

(a) Hodgkin's lymphoma **(b) Cervical cancers**

(c) Lung carcinoma **(d) Kaposi's sarcoma**

4. Promontary sign is seen in

(a) Kaposi's sarcoma **(b) Angiosarcoma**

(c) Benign vascular tumors **(d) All of the above**

5. In AIDS associated Kaposi's sarcoma patients without Anti Retroviral Therapy, the mortality is

(a) 100 % **(b) 90%**

(c) 80% **(d) 50%**

Answers

1. c **2. d** **3. b** **4. d** **5. b**