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Review Article

A Comprehensive Review: Advances in Studying and Healing Kaposi's Sarcoma

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A B S T R A C T

Kaposi's sarcoma (KS) is an uncommon, malignant, multilocular vascular disorder with a predominance of the skin and mucous membranes, lymphatic system, and internal organs such as the gastrointestinal system, lungs, or liver. There are five major epidemiologic subtypes of KS, each of which has its own clinical course, prognosis, and tendency to occur more frequently in a certain population: There are five distinct KS types: There are five different types of KS: classical, iatrogenic, immunosuppressive, endemic (African) lymphadenopathic, epidemic, Aids-related, connected to immune reconstitute inflammatory syndromes (IRIS), and KS in men who have sex with men (MSM) but aren't HIV positive. This interdisciplinary guideline condenses the most recent recommendations for diagnosing and treating the various kinds of KS.

Keywords: Kaposi's Sarcoma (KS), HIV, Human Herpesvirus 8 (HHV-8), Classical KS, KSHV, AIDS-KS, Lymphoma

Introduction

The sarcoma of Kaposi (KS), also known as "Idiopathic Multiples Pigmentsarkom der Haut," was initially reported by Moriz Kaposi in 1872.[1] Originally from Kaposva'r, Hungary, Kaposi (1837–1902) later joined the University of Vienna's dermatology faculty. In 1871, he legally changed his name from Moritz Kohn and wed the daughter of Ferdinand von Hebra, the department's professor and head, whom he eventually succeeded. The initial 1872 account of five patients by Kaposi closely resembles the Kaposi's sarcoma observed in AIDS (AIDS-related KS), rather than the classic form of KS typically seen in older men of Italian, Middle Eastern, or Jewish ancestry, who generally exhibit a mild disease course. All five of his patients died within two to three years. "Based on what we have seen, this disease appears to be fatal and incurable from the outset," Kaposi wrote.[2]

KS has four primary epidemiological types that are now well-acknowledged. Classic KS, also known as sporadic KS, is the variant of KS that Kaposi first identified. In contrast to the cases first described by Kaposi, classic KS mostly affects the skin on the legs and is most common in older men of Middle Eastern or Jewish ancestry. Beginning in 1947, a number of publications documented KS instances in Africa, including lymphadenopathic KS cases in children (ages 2-4); these KSs are currently typically referred to as inherent KS.[3,4] In 1994, KS Human herpesvirus-8 (HHV-8) and the herpes simplex virus (KSHV) were discovered, revealing the cause of the diseases for the first time. Epidemiologic evidence suggested that this malignancy was caused by an infection that wasn't caused by HIV at the time.[5]

Although AIDS-related KS or iatrogenic KS are connected to clearly specified immunodeficiencies, known as decreased immune function in classic KS, believed to be

connected to "immunosenescence"—that has been, an ageing resistant system or inherent KS, thought to be connected to chronic infection and hunger, is not well characterised. In addition to KS, KSHV also causes primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD), two lymphoproliferative diseases.[6,7] In order to test novel anti-angiogenic drugs, one of the primary targets for the metastatic processes in which both tumour cells and enhanced vascular proliferation are necessary, KS is regarded as a model for angiogenesis. A deeper understanding of the viral gene networks implicated in tumorigenesis may also be useful for better managing the apoptotic abnormalities that are likely found in KS cells.[8]

Epidemiology

The epidemiology of KS in the US is primarily AIDS-KS compared to MSM and traditional KS among the elderly, which occurs in a region with low frequency of KSHV and HIV, and high-risk populations. In the recent past, only male instances were mentioned since female patients made up just 6% of all cases. First, in an area with low KSHV seroprevalence, as a crude proxy to differentiate between conventional KS and KS linked with HIV, KS cases are divided by age category (65 and 65+). Today, younger boys are experiencing cases of development almost as regularly as older guys. After the year 2000, there was no longer a decline in the occurrence of AIDS-KS as both KSHV and HIV are now common in the US population. Dermatologists and oncologists will continue to examine and treat KS lesions.[9,10]

HIV seroprevalence and AIDS-KS, as well as inherent KS in the elderly and young, are what drive the KS epidemiology in South Africa and Sub-Saharan Africa, a region with high KSHV prevalence and significant HIV seroprevalence. KSHV prevalence was high in this area before HIV emerged, and transmission occurs from mother to child in both adult and paediatric populations World Health Organization (WHO) GLOBOCAN data and several other studies reveal that Kaposi's sarcoma continues to account for a significant proportion of the total cancer incidence in sub-Saharan Africa, including 24% in Mozambique, 27% in Uganda, and 35% in Zimbabwe. This is despite the difficulty in locating high-quality incidence data.[9,11,12]

Aetiology

Since the 1950s, it has been believed that viral agents play a significant part in the growth of KS, which results from complicated and multifactorial processes, including immunosuppression.[13] A specialised role for herpesviruses was hypothesised in the 1970s. Giraldo and colleagues discovered that five out of eight tissue cell types cultured from African patients with Kaposi's sarcoma contained herpesvirus-like particles, which led to the identification of the genomic sequences of cytomegalovirus (CMV) in these tumors. The aetiology of KS experienced a significant advance in 1994, according to reports. By using representational difference analysis, Chang and colleagues[14] discovered HHV-8, a novel human herpesvirus and found it even those unrelated to HIV, in over 90% of KS lesions. Over 95% of KS patients have one of the four types of KS and have now been shown to have HHV-8. Similar to how other herpesviruses spread, HHV-8, which is discovered in the saliva and semen, can also be transmitted through kissing and saliva contact. Age-related increases in HHV-8 antibody prevalence are seen, as are significant regional variations. North Europe and the Americas have low HHV-8 seroprevalence rates (5%), Sicily has high rates (35%) and Botswana has extremely high rates (87%) of seroprevalence. The rates are frequently correlated with the KS prevalence. However, some nations, including Thailand, the Gambia, the Ivory Coast, and Brazil all have low KS incidence and high HHV-8 seroprevalence.[14]

Pathophysiology

The endothelial origin of KS helical tumour cells supports earlier research that relied on histochemistry and ultrastructural results. Early KS lesions are thought to be caused by the circulation of endothelial and mononuclear "progenitor cells" By upregulating many lymphatic-associated genes such as podoplanin, LYVE1 (lymphatic vessel endothelial receptor) and cerebrovascular endothelium growth factor receptor 3 (VEGFR3), HHV8 infection changes the body's plasma vessels, their resemblance to lymphatic endothelium. However, HHV8 infection alone doesn't seem to be enough for KS to manifest. The growth of KS is also dependent on the local inflammatory environment and some degree of host immunological dysfunction.[15]

During the development of the KS, there is an upregulation of many crucial HHV8 gene products, including latency-associated atomic antigens (LANA-1 or LNA-1). The HHV8 herpesvirus has developed a range of defences versus the host immune system and, like other herpesviruses, is inactive within cells. The growing comprehension of the numerous molecular pathways linked to the evolution of KS has stimulated a number of clinical investigations utilising cutting-edge therapeutic drugs.[16]

Histopathology

The several epidemiologic KS kinds have roughly the same histology. However, several investigations have shown small histopathologic variations between AIDS-KS and occurrences of KS not connected to HIV; these variations include the prevalence of mitosis- and cellular anaplasia in HIV-negative individuals and the tendency of AIDS-KS lesions to have longer dissecting vessels. The dermis is dissected by aberrant arteries accompanied by thin endothelial cells in

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the early patch stage of KS. The so-called promontory sign is caused by ramifying proliferating vessels that frequently surround bigger ectatic arteries and epidermal adnexa. This symptom has been noted in other vascular diseases, such as mild vascular tumours and angiosarcoma, thus it is not pathognomonic for KS. In patch KS lesions, hemosiderin-rich macrophages, red blood cells that have extravasated and a lack of long-lasting inflammatory cells are frequently found. These early histologic alterations might be subtle, making a biopsy difficult to detect.[17]

Spindle cell and vascular proliferation characterises plaque-stage KS lesions, they mostly affect the dermis and sporadically the subcutis in the skin. Fully established KS tumours are composed of several fascicles of these spindle-like tumour cells, and they are typically accompanied by a variable chronic inflammatory infiltration composed of plasma cells, lymphocytes, and dendritic cells. Additionally, KS lesions have a number of macrophages that are hemosiderin-loaded. This is not shocking considering that iron seems to have a role in the aetiology of KS. KS may be distinguished from iron-deficient interstitial granuloma annulare lesions by iron staining. Spindle cells in KS nodules are transected, creating gaps between them that resemble sieves in cross-section. These spindle cells are often seen in cohesive clusters with a bloody backdrop in fine-needle aspiration specimens.[18] Advanced KS lesions frequently have these globules, which are eosinophil and periodic acid-Schiff (PAS)-positive. They can be detected externally or inside lesional cells.[18]

Under electron microscopy, lesional cells occasionally exhibit Weibel-Palade aggregates and intra-fragmentary erythrocytes, which are assumed to correspond to the hyaline globules seen under a light microscope. The usual KS lesions lack a substantial amount of mitosis graphs, necrosis, or cellular pleomorphism. Concomitant pathologic abnormalities, which are commonly brought on by an opportunistic infection (such as cryptococcosis, mycobacterial granules or molluscum contagiosum), may occasionally be seen in AIDS-KS lesions.[19]

Clinical Features

AIDS-related the clinical history of KS varies, ranging from mild mucocutaneous illness to extensive organ involvement. Visceral organs, salivary glands, lymph nodes, and skin may all be affected by the lesions. Skin diseases are how most people first show up. On rare occasions, visceral illness might appear before cutaneous signs. Almost all organs have been affected by lesions, according to autopsy data. However, the brain is unharmed.

Nearly all patients have cutaneous lesions, with most exhibiting the following features:

- Usually multicentric in a continuum of development; several skin lesions.
- **Tumour-associated lymphedema:** This condition, which typically affects the lower extremities or the face, is considered to result from the blockage of lymphatic pathways.
- Walking-related pain from lesions affecting the soles of the feet

Anywhere in the digestive tract might experience gastrointestinal lesions. The majority of lesions are clinically indolent and asymptomatic. Typically, gastrointestinal illness is a sign of an HIV infection that has progressed further. Among the symptoms are the following:

- Dysphagia and odynophagia
- Vomiting, nausea, and stomach discomfort
- Hematochezia, melena, and haematemesis
- Stomach obstruction

It could be challenging to discern between pulmonary involvement and opportunistic infections. Among the symptoms are the following:

- Chest discomfort, dyspnoea, haemoptysis, and cough
- Pulmonary lesions may be a radiological finding without any symptoms.
- Pleural effusions frequently produce blood and exudate.

Oral involvement in KS can take many different forms, from isolated spots to nodules and swellings that bleed, hurt, and are necrotic. Red to purple lesion symptoms may appear in the buccal mucosa.[20]

Diagnosis

Recent investigations have proven the poor predictive usefulness of KS clinical diagnosis, despite the fact that KS can be strongly suspected in a suitable clinical scenario. Although histological confirmation of a KS diagnosis continues to be the benchmark, making the prognosis is sometimes difficult, particularly if pathologists are unfamiliar with the range of KS's histopathological characteristics. The pathologist's ability to detect minuscule characteristics that are simple to miss is crucial to the histopathology diagnosis of early-stage KS. But confirmed clinical lesions of KS frequently, though not always, display specific histological features that enable a knowledgeable histopathologist to make an exact diagnosis.[21]

Patients with KS should be screened for HIV and assessed for underlying immunodeficiency. Patients with a known HIV infection should have the numbers of CD4 cells or plasma HIV viral-load assays done. Faecal occult blood tests should be performed on patients with AIDS-related KS in order to check for any potential gastrointestinal involvement.[22]

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The following laboratory tests are advised:

C-reactive protein, viral load of KSHV/ HHV-8, interleukin-6 (IL-6) or IL-10 and serum protein electrophoresis (SPEP)[23]

Imagery Researches

Chest Radiography

A chest X-ray is advised for all patients with KS linked to AIDS in order to determine whether the lungs have been affected. The following radiographic features may be seen in KS and are varied and nonspecific:[24]

Hilar or mediastinal lymphadenopathy, interstitial infiltrates, pleural effusions, diffuse reticulonodular infiltrates, and an isolated pulmonary nodule

Scans using Gallium or Thorium

These investigations could assist in distinguishing between infection and KS of the lungs. Infections are commonly thallium-negative and gallium-avid, in contrast to the characteristically intense thallium uptake and lack of gallium uptake of pulmonary KS lesions.

This differentiation is less of an issue now that highly active antiretroviral therapy (HAART) has been developed. Before then, there had been an increase in the occurrence of *Pneumocystis jiroveci* pneumonia (PCP), KS, malignant lymphoma, *Mycobacterium avium* intracellulare (MAI), and tuberculosis (TB).

Thorium-positive and gallium-negative scanning patterns' specificity, sensitivity, affirmative potential for prediction, and negative predictive value were 63%, 95%, 92%, and 75%, respectively.[24] This type of study has minimal clinical importance, hence the diagnosis needs to be made according to more clinical reasons.[24]

Procedures

The following procedures are used to diagnose Kaposi's sarcoma:

Punch biopsy: to make a certain diagnosis, a biopsy using an unwelcome punch of skin tissue or a transbronchial, pleural, or endoscopic biopsy is necessary. The usual histologic findings include extravasated red blood cells, spindle cell development, and obvious slit-like vascular gaps.

When performing a bronchoscopy, pulmonary involvement is frequently detected by a mild elevated cherry-red lesion (submucosal). Due to the possibility of bleeding, biopsies are often avoided.

Colonoscopy or esophagogastroduodenoscopy (EGD): Gastrointestinal lesions are commonly seen during these procedures. Due to the submucosal position of many lesions, the result of endoscopic sampling may be minimal.[25,26]

Management

There is currently no medication to cure HHV-8 infection. Therefore, KS cannot be cured. Instead, in every instance of KS, the aim of therapy is to reduce symptoms and stop the spread of the illness. Decisions on treatment rely on the kind of KS, the existence of symptoms, and the severity of the illness.

Compression stockings can be used to treat lower extremity oedema. Local treatments can be applied to the treatment of bothersome or ugly lesions, such as surgical excision, radiation, cryotherapy, and intralesional chemotherapy. Only individuals with advanced illness or those who have failed local treatment should get systemic chemotherapy.[27]

Antiretroviral Therapy for KS related to AIDS

The first stage of treatment should include the best possible HIV infection control utilising HAART for AIDS-related KS. The response to HAART may range from 20 to 80%[28] depending on the severity of the infection & the quantity of pretreatment. Since it first became available, HAART has changed the goal of treatment for KS from short-term palliation to long-term remission and control. Most successful combination antiretroviral therapies use two nucleotide enzyme inhibitors (NRTIs) and a protease inhibitor (PI), which is or non-nucleoside reversed transcriptase inhibitor (NNRTI). Although level 1 clinical data are currently lacking to corroborate this, there is some speculation that angioproliferative KS-type diseases may directly combat cancer.[29]

Regarding how KS responds to antiretroviral regimens, there is no difference between PI-based and NNRTI-based antiretroviral regimens.[30] If a disease is not visceral, HAART may be used as the only treatment option. Chemotherapy might be added in cases with visceral illness. Radiation treatment may be used for diseases with local symptoms.[31]

However, HAART alone is rarely effective in treating people with KS, which has a low prognosis. Additionally, 3 to 6 months after restarting ART, immune reconstitution inflammatory syndrome (IRIS) is seen in 3–39% of individuals with KS associated with AIDS and deterioration of their condition.[32] Increases in CD4 levels and the management of HIV viraemia are related to this.[32] The following are the requirements for KS IRIS according to the AIDS Clinical Trial Group:

- Increase in CD4 count by at least 50 cells/L or a 2-fold increase, and a reduction in HIV-1 viral load of more than 0.5 logs after beginning, restarting, or changing the HAART regimen
- KS progressing more quickly than anticipated within 12 weeks of starting HAART

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Pulmonary involvement, concurrent use of glucocorticoids, or recent use of glucocorticoids are risk factors for KS-associated IRIS Because they stimulate KS spindle cells, glucocorticoids are often contraindicated in this condition.[33] Chemotherapy may be required in this clinical scenario to treat the illness and slow its development.

The severity of the illness, the presence and nature of signs, the rate at which the illness is progressing, and the total and therapeutic objectives all must be taken into consideration when determining the next course of treatment after HAART. Visceral diseases that are symptomatic or life-threatening, mucocutaneous diseases that are fast progressing and have pain or ulceration, or symptomatic lymphedema should all get palliative systemic treatment. There aren't many accurate estimations of the response rate with just HAART in this situation compared to combination chemotherapy with HAART. In a South African study, HAART alone had a response rate of 39% whereas HAART + chemotherapy had a response rate of 66%. Furthermore, within a year of being randomised, 35% of the individuals in the HAART group required palliative chemotherapy or radiotherapy. These results suggest that HAART and chemotherapy be utilised in patients with substantial tumour volume (T1).[34]

Resonance Therapy

The most popular and successful local treatment is radiation therapy.[35] It can relieve discomfort, bleeding, and unattractive blemishes. The reported response rates for KS range from 68% to 92%. An 87% complete response rate was seen in 30% of treated locations, according to a study evaluating the effectiveness of 97 epidermal KS lesions that had not been treated before receiving radiotherapy.[36]

Different radiation kinds and dosages are employed depending on the lesion's location, depth, and diameter. Low-voltage photon or electron beams (of up to 100 kV) are one alternative for radiotherapy. Studies have demonstrated that hypofractionated regimens, such as 20 Gy in 5 fractions, are as effective as the standard regimen of 24 Gy in 12 fractions.[37] In addition to radiation-induced mucositis, patients with HIV are more prone to have hyperpigmentation in the desquamation of and ulceration of treated lesions.[38,39]

Surgery Excise

Patients with tiny superficial lesions may benefit from surgical excision. Local recurrence is the key issue. Clear surgical margins are not always indicative of KS eradication, completely eliminated at a specific anatomical location. Local recurrence occurs often. But over a long period of time, a number of minor excisions may be a sensible strategy to accomplish effective disease management. Patients experiencing a gastrointestinal crisis, such as obstruction or haemorrhage, or with excruciatingly painful, localised lesions may potentially benefit from surgery. Its use in AIDS-associated KP is constrained by the danger of HIV infection to the operating room staff.[39]

Intralesional Chemotherapy

The usual kind of KS, with the predominance of the localised cutaneous disease, where the vinca alkaloid compounds, low-dose vincristine or vinblastine, with bleomycin, are often used. Responses last for 4-6 months and happen in 60–90% of individuals with few systemic adverse effects. Three to four weeks separate doses are spaced out at a dosage of around one-tenth the systemic dose of the medication. Changes in pigmentation, oedema, blistering, ulceration, discomfort during the injection, and localised but often passing neuropathic sensations are all possible side effects.

Intralesional chemotherapy is only sometimes used since the illness recurs elsewhere. Additionally, systemic vinca alkaloid treatment could be just as successful and result in less localised skin harm.[40]

Conclusion

It has been proven that HHV-8 infection causes KS, which is more common in people with HIV infection, immunosuppression, and ancestry from Eastern Europe or the Mediterranean. The primary care team should take extra precautions to undertake comprehensive skin checks in individuals with seropositivity who are most susceptible to acquiring KS in order to search for distinctive violet-coloured plaques and patches. Furthermore, individuals in these high-risk categories should be advised to check their skin for lesions as well. Any worrisome lesions should elicit a pathologist's quick sample and inspection. The submitting physician should provide the reviewing pathologist with a thorough clinical history and inform them know there is a chance that the patient has KS.

Conflict of Interest: None

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