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Kaposi's sarcoma revisited

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Abstract

Kaposi's sarcoma is a puzzling condition of unclear, possibly endothelial origin. It is divided into four distinct types regarding the affected population: classic in elder men of Ashkenazi Jewish and Mediterranean origin; endemic in African infants and young males; iatrogenic in patients under immunosuppressive regimens; epidemic in men having sex with men affected by AIDS. The exact etiopathogenesis of Kaposi's sarcoma continues to elude its researchers. Nonetheless, it has been discovered that human herpesvirus 8 is essential but not sufficient for sarcoma development. Also, iron exposure of populations inhabiting regions with volcanic soils has been suggested to play a pivotal role in the classic and endemic Kaposi's sarcoma etiology. The epidemic Kaposi's sarcoma is strongly associated with HIV's detrimental effect on immune system and HIV's Tat protein pro-angiogenic properties. Because Kaposi's sarcoma is found also in men having sex with men without AIDS, it has been proposed that certain lifestyle features (e.g. massive semen exposure and inhalant nitrites) may promote transformation of endothelial cells of both lymphatic and vascular origin. Despite numerous studies on Kaposi's sarcoma, it continues to be an incurable disease. The therapeutic approach includes local treatment and systemic administration of cytotoxic, immunomodulator and antiviral drugs. Because of the increasing prevalence of Kaposi's sarcoma, especially in certain parts of Africa, a better understanding of this condition is necessary. **(AIDS Rev. 2007;9:230-6)**

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Key words

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Introduction

In 1872 in Vienna, a Hungarian dermatologist Moricz Kaposi described an unusual neoplasm that affected elder men[1]. Since the lesions consisted of reddish, purple or brown plaques, macules or nodules, he denominated his finding "*sarcoma idiopathicum multiplex haemorrhagicum*". As histologic techniques developed, it became clear that a characteristic finding in Kaposi's sarcoma (KS) nodular lesions – but for extravasated erythrocytes, macrophages rich in hemosiderin and neoangiogenesis – are so-called spindle cells. However, the spindle cells resemble macrophages, smooth muscle cells, dendritic cells, and endothelium of both vascular and lymphatic origin[2,3]. Moreover, a century after Dr. Kaposi's description, this poorly understood neoplasm has been encountered in very distinct groups of patients and thus classified into four discrete types. Still, it continues to divide researchers as to its etiopathogenesis, supposed malignant character and, therefore, management.

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Types and epidemiology

Kaposi's sarcoma is a very heterogeneous group of neoplasms that is usually divided with regard to its clinical and epidemiologic characteristics into four types described below[4].

Classic

Known also as chronic, European, or sporadic, this form mainly (in 90% of cases) affects males over 60 years old of Ashkenazi Jewish and Mediterranean origin. The male-to-female ratio is 10-13:1. The European regions with the

highest incidence include Sicily and Sardinia[5,6]. It is virtually not found in the USA nor is it related with an infection by HIV. Nevertheless, it may be associated with malignant neoplasms and disorders of the immune system. Since the lesions localize mainly on the lower extremities and affect the skin and the subcutaneous tissue only, sporadic KS does not significantly shorten lifespan. However, some forms are found in younger patients, or have an aggressive course[7].

Endemic KS

This type is divided in two subtypes[8]. In the first one, usually skin involvement is observed with only local aggressiveness and sometimes massive edema. The affected populations are middle-aged adults (25-50 years old) residing in several sub-Saharan countries such as Uganda, Sudan, Democratic Republic of Congo, Rwanda, Burundi, as well as Malawi, eastern Zaire and the coast of Cameroon[9,10]. In these regions, KS comprises up to 17% of all neoplasms in adult males and it is the second most common cancer in women.

The second subtype of endemic KS affects mainly Bantu children under 10 years of age. It is diagnosed due to generalized lymphadenopathy, especially pronounced in the cervical region. The pediatric-endemic KS being lymphadenopathic, the differential diagnosis should include the Mikulicz syndrome (dacryosialoadenopathy)[8]. It has a much more serious course than in adults and often terminates fatally within two years after the diagnosis[11]. Unlike the epidemic one, African KS has increased importantly in incidence[12].

Transplant-associated KS

Solid organ transplant recipients have from 500- to 1000-times higher risk of developing KS than the general population; depending on the country, KS prevalence varies from 0,5%[13] to 5%[14] of allograft recipients. It may develop within months after starting the immunosuppressive therapy (particularly with calcineurin inhibitors) and, in most cases, only cutaneous changes are present. Nonetheless, up to 45% of the recipients have visceral involvement which, as mentioned above, is associated with poor prognosis[15].

Epidemic KS

By July 1981, the Centers for Disease Control (CDC) described 26 homosexual men from California who presented lesions typical of KS[7]. The course of the disease was aggressive and 31% of the patients died within two years of diagnosis. Furthermore, a biopsy examination confirmed *Pneumocystis jiroveci (carinii)* pneumonia in 16% of these patients. Since these men had also numerous opportunistic infections, the clinical picture was soon recognized as "gay compromise syndrome"[16], later renamed as AIDS due to the stigmatizing name and a few similar cases found in heterosexuals. The incidence of KS varies among groups of patients with AIDS (PWA): 21-40%[17] of men having sex with men develop KS in contrast to only 1.6% of pediatric PWA and 1% of hemophiliac PWA[17]. Regardless of the differences in prevalence, KS in PWA is usually very aggressive, lacks a specific localization, and frequently involves the gastrointestinal tract, lungs, lymph nodes, and other organs. Around 30% of PWA with KS eventually develops a malignant neoplasm such as lymphoma.

Recently, the AIDS Clinical Trials Group developed a staging system for predicting survival and treatment outcome in PWA with KS[18]. The system is based on the tumor burden, presence of concomitant systemic illnesses, and immune status. A reevaluation of this staging system showed that after the advent of HAART, of clinical utility was only tumor burden and systemic illnesses[19].

KS etiopathogenesis

HIV and multifactorial theory

Kaposi's sarcoma has been subject to thorough investigations and numerous studies aimed to answer the question of its accurate etiology. Since, in 1983, a retrovirus, subsequently named the human immunodeficiency virus (HIV), was cultured from T-cells of a homosexual man with lymphadenopathy[20], the majority of scientists were of the opinion that it was HIV that made mesenchymal tissue undergo a metaplasia and form sarcoma. Nevertheless, as early as in 1984 it became apparent that HIV was absent in the KS cells, and hence it was unlikely to cause the lesions directly[21]. Nowadays it is assumed that the HIV-1 Tat protein (a product of the transactivator gene) acts as a cofactor in KS development by stimulating angiogenesis[22]; the studies of its antiapoptotic effect in different types of cells seem contradictory[23,24]. Since HIV was discarded as a unique cause of KS, the research focused on identifying an unknown infectious agent presumed responsible for this disease. However, in 1982 some substances – such as inhalant nitrites and other so-called "street drugs", all commonly used by the 26 homosexuals – were discovered to be risk factors for developing KS[25]. Furthermore, it should be noted that a few homosexuals

developed KS with no signs of immune deficiency or HIV infection[26]. On the basis of this highly intriguing finding, and the fact that in Africa the incidence of KS among prostitutes and mothers is low and resembles the world's average, some scientists decided to follow the noninfectious pattern and proposed a multifactorial etiology[27]. According to their conclusions, KS in homosexuals develops due to the use of inhalant nitrites and due to the exposure of lymphatic and vascular endothelium to semen that takes place during passive anal intercourse. Since both of the substances have a strong oxidative potential, they may cause mutations and subsequently induce, or at least promote, carcinogenesis. The spermatozoa alone have indeed an interesting potential of transforming agents and were found to induce cancers in both human[28] and rodent tissues[29]. However sound this theory seems, it does not explain the significant differences in the geographic distribution of Kaposi's sarcoma, its declining incidence in PWA since the advent of HAART[30], and its presence in post-transplant patients. The two latter questions were answered in 1994, when a previously unknown viral DNA was found in KS lesions of PWA[31].

Human herpesvirus-8

The identified virus has been classified as a human herpesvirus type 8 (HHV-8) and is also known as Kaposi's sarcoma-associated herpesvirus (KSHV) (Table 1). The HHV-8 turned out to have unique features. Namely, most of its genes are homologous to cellular oncogenes and as a result enable it to alter the cellular cycle, inhibit apoptosis, evade immune mechanisms, and induce angiogenesis. Among the most important HHV-8 genes is the open reading frame 74 (*ORF74*) which encodes for the viral G protein-coupled receptor (vGPCR) during the lytic phase[32]. This protein, a homolog of the human interleukin-8 (IL-8) receptor, shows constant downstream activity and at the same time it can be activated by the IL-8 and growth related protein-α[33]. As a result of vGPCR signaling, vascular endothelial growth factors are induced and therefore neoangiogenesis occurs[34].

Other viral lytic genes include *ORFK6*, *ORFK4* and *ORFK4.1*. Their products (vCCL1, vCCL2 and vCCL3) demonstrate partial homology to macrophage inhibitory proteins and may act as agonists of endogenous chemokine receptors[35]. Besides their blocking effect on the immune system, vCCL were found to promote angiogenesis in chick chorioallantoic membrane[36].

The *ORFK2* encodes for a viral homolog of IL-6, which assures a higher proliferation rate in infected cells as compared to noninfected ones[37]. Furthermore, HHV-8 is capable of inducing endogenous IL-6 via the vGPCR and a transcriptional activator of lytic genes (RTA)[38], and thus promoting angiogenesis.

Table 1. Human herpesvirus-8 general characteristics[94]

Genus	Rhadinovirus
Genome length	165 kb
Genome form	Circular in latent infection, linear in lytic phase
Number of subtypes	6 (A, B, C, D, E, N)
Diameter	120-150 nm
Capsid	Icosahedral heterotetramer
Envelope	Lipid bilayer
Target cells	Epithelial and endothelial cells, lymphocytes, keratinocytes, marrow stromal cells
Reservoir	B-cells and monocytes
Cellular receptor	Heparan sulfate
Infection	Latent prevails in Kaposi's sarcoma; lytic in multicentric Castleman's disease, primary effusion lymphoma
Associated diseases	Kaposi's sarcoma, multicentric Castleman's disease, primary effusion lymphoma

The HHV-8 latent genes play a more important role in the pathogenesis of KS because the virus usually infects endothelial cells in the latent form[39], and also it is this form that induces the tumor growth and cellular proliferation[40]. The most well-known latent gene is *ORF73,* which encodes for the latency associated nuclear antigen (LANA)[41]. This protein, besides being a transcriptional regulator that modifies expression of both viral and cellular genes, has been shown to enable the virus to persist in the target cells as episome. Furthermore, it has been suggested that the LANA-1 structural features impede its presentation with the major histocompatibility complex. As a result, HHV-8 latently infected cells might evade immune responses[42]. The LANA-1 antigen (LNA-1) is used to confirm the diagnosis of KS[43].

Among other crucial genes of HHV-8 are the following: viral homolog of *bcl-2*[44], which allows the infected cells to inhibit the proapoptotic signaling[45]; a similar effect is exerted by the product of *ORF71* – a viral inhibitory protein of Fas-associated death domain-like IL-1β converting enzyme[46]; finally, a viral homolog of the cellular cyclin D

inactivates the phosphorylation of retinoblastoma protein and as a result alters the cellular cycle regulation leading the infected cells directly into the S-phase[47]. Because its DNA is found only in late, already hyperplastic/malignant KS lesions, some investigators argue that HHV-8 is not a transforming virus[48]. The fact, however, that HHV-8 has been associated with other malignancies (i.e. multicentric Castleman's disease and primary effusion lymphoma) makes this statement uncertain and stresses the need for developing more effective anti-HHV-8 drugs.

Isolation of HHV-8 provided a feasible explanation for KS associated with transplants, as well as for the decrease of KS prevalence in PWA since the introduction of HAART. With very few exceptions[49], the virus can be considered necessary for the development of every type of KS. However, it most certainly is not a sufficient factor because, in the USA in the 1970s, KS occurred in 1 male out of 17,000 infected[50] (assumption based on a 5% seroprevalence and KS incidence rate 0.3/100,000). Although the global seroprevalence of HHV-8 is estimated to be around 2-10%[51], it shows significant fluctuations, from 0-5% in Northern Europe, North and South America[52], and 35% in Sicily[53], to 87% in Botswana[54]. Thus the geographic fluctuations of HHV-8 seropositivity seem closely related to the prevalence of KS[55]. Nevertheless, there are regions, such as Brazil, Northern Thailand, Gambia and the Ivory Coast, with high seropositivity rates in which endemic or epidemic KS either has not been reported or is extremely rare[56-58].

Iron and other minerals

As mentioned above, the question of KS distribution remained unaddressed until an interesting observation was made by Ziegler who noticed the relation between KS, podoconiosis, and the vicinity of volcanic soils[59]. Both podoconiosis and endemic KS share similar geographic distributions in the vicinity of volcanic soils rich in aluminum, silicon, and iron[60]. Furthermore, the most prominent sign of both conditions is lymphedema of the lower extremities, presumably caused by the fibrogenic effect of silicon compounds, and thus involvement of the lymphatic vessels seems obvious. Another common feature of the regions of high incidence of both the epidemic and endemic KS (i.e. the East African Rift[9], Sicily and Sardinia[61], the Faroe Islands and Iceland[62]) is the presence of iron-rich volcanic, mafic minerals in the clay soil. In a big part they are made up of colloidal solution of kaolinite. Ultrasmall particles of this mineral may enter the skin by sweat glands ducts, and thanks to a negative charge, they may bind metallic cations[59]. Aluminum hydroxide is thought to start an immunologic response by stimulating the complement, macrophages and the secretion of IL-1[63], all characteristic histopathologic features of KS. However, a more prominent role seems to be played by iron, which has been described as a potent inducer of carcinogenesis in both animals[64] and humans[65,66]. Iron contributes to carcinogenesis in a complex manner, which includes such phenomena as enhancing viral nucleic acid production[67], augmenting the mutation rate of tumor suppressor genes via reactive forms of oxygen generated in the Fenton reactions[68], inhibiting the immune responses of CD4 cells and macrophages[69], leading to the inhibition of apoptosis in endothelial cells[70], activating transcription factors like nuclear factor kappa B and activator protein-1 and promoting the expression of IL-6[71,72], and functioning as a cofactor of ribonucleotide reductase thus allowing for an accelerated DNA synthesis. Furthermore, it has been demonstrated by Simonart, et al. that iron salts stimulate growth of KS cells *in vitro*[73], while iron chelators lead to their apoptosis[74]. Also, Simonart suggests that extravasated erythrocytes, so characteristic of KS, may serve as a continuous source of iron at the lesion site. Similarly, he points out that lower iron reserves might explain the lower KS prevalence among women and the disappearance of KS lesion during or after pregnancy[75]. However, a study on nude mice points rather to a hormonal influence that is exerted on KS cells during pregnancy by the beta-chain of human chorionic gonadotropin[76]. Moreover, high similarity in amino-acid sequence of the beta-chain of human chorionic gonadotropin to the beta-chain of luteinizing hormone[77] (cyclically present at high concentrations in non-pregnant mature women) may help to explain the lower incidence of KS in women in terms of hormonal differences between the sexes.

Insects and saliva

In HHV-8 transmission, which is far from being completely understood, two factors are thought to play an important role: blood-sucking insects and saliva. Arthropods are taken into consideration because of an interesting observation according to which the incidence of age-related KS lowered after anti-malaria DDT spraying in Italy's malaria regions[78]. Also, it has been observed that in Uganda the KS incidence is directly related to the frequency of insect bites[79]. However, the relation between blood-sucking insects and KS remains controversial.

On the other hand, the role of saliva in both sexual and nonsexual HHV-8 transmissions seems confirmed because saliva, unlike other body fluids, was proved to contain high concentration of viral particles[80] due to viral shedding by

oral epithelial cells. The facts that saliva viral shedding is independent of $CD4^+$ count[81], and thus may occur early after the HHV-8 infection, and that oro-anal sexual contacts were found to be associated with HHV-8 acquisition[82] make saliva an important factor for HHV-8 transmission among men having sex with men.

Treatment of KS

Because of the heterogeneity, there are no standard therapeutic guidelines for the treatment of KS. Usually, the therapy depends upon the patients' general condition, the type of KS, and the severity of the disease (such as the size of the lesion and visceral involvement). The best therapeutic results are obtained in the classic KS with only local treatment. Transplant-associated KS usually withdraws after the reduction of the immunosuppressive therapy; however, this may lead to graft rejection in as much as 50% of cases[83]. Endemic KS normally requires a systemic therapy with cytostatic agents; unfortunately, the least favorable outcome is seen in the most numerous group of patients with the KS (i.e. epidemic type) and the disease management in PWA should aim at maintaining quality of life.

Local treatment of KS

Local treatment allows for a safe, cost-effective therapeutic approach. Although it has few side effects, the recurrence rate is significant. The most popular techniques include: cryotherapy with liquid nitrogen for skin lesions; radiotherapy, which seems the best option for treating large tumors in the oral cavity or lymphedema of the lower extremities; photodynamic as well as laser therapy that seems useful in oral lesions; and intralesional chemotherapy with vincristine or vinblastine[8,84]. An interesting topical therapy has been developed by Walmsley, et al. who successfully used alitretinoin for cutaneous lesions in epidemic KS[85]; nevertheless, some researchers found alitretinoin ineffective for treating patients with the classic KS[86]. Of lesser significance is the surgical approach that can be only beneficial for patients with solitary lesions.

Systemic treatment of KS

The epidemic KS prevalence has decreased dramatically since the introduction of HAART[30]. Because of its beneficial effect on the course of epidemic KS, HAART remains a basic therapy for PWA with KS. Since protease inhibitors and nonnucleoside reverse transcriptase inhibitors were demonstrated to have similar efficacy, the effect of HAART is exerted rather by restoration of patients' immune status than by any direct antiviral activity[8].

Among antiviral drugs, foscarnet, ganciclovir, cidofovir, and adefovir are considered to have anti-HHV-8 activity. However, the studies on the HHV-8 sensitivity to these drugs have often shown contradictory results[84].

In case of visceral involvement, symptomatic course or fast progression of KS, cytostatic drugs and interferon-α (IFNα) are used. The chemotherapeutic used in first-line therapy is pegylated liposomal doxorubicin, but also other liposomal anthracyclines (e.g. daunorubicin) are used. The pegylated liposomal drugs have been shown to be not only as effective as standard cytostatics, like vinca alkaloids, bleomycin or Adriamycin and etoposide, but also significantly less toxic.

Since the etiological factor of all types of KS is a herpesvirus, IFNα and IFNβ were thoroughly studied in relation to their use in KS therapy[87]. Interferon-α is the immunomodulator that has been proved to lead to a decrease of tumor burden in PWA[8]. However, the treatment with IFNα must not be interrupted in these patients because of the recurrence rate high and frequent development of refraction to the treatment. Surprisingly, low doses of IFNα have been shown to be effective in the classic KS therapy, where the recurrence of lesions was rare and the retreatment highly successful[88].

Paclitaxel, a microtubule stabilizer with proapoptotic properties[89], has also been found useful in KS therapy, particularly epidemic-type KS. Although it is well tolerated, it produces neutropenia and this limits its use to a second-line therapeutic agent in treatment of PWA in the USA[90].

Recently, a novel use of angiotensin I converting enzyme inhibitors and of angiotensin II type 1 and type 2 antagonists in cancer treatment has been described[91]. Furthermore, some studies showed their efficacy in the treatment of classic KS[92].

Detailed review of KS therapy lies beyond the scope of this paper. A comprehensive review of the KS treatment, including therapeutic agents under investigation, may be found elsewhere[8,84,93,94].

Conclusions

The Kaposi's sarcoma etiopathogenesis has been greatly elucidated and new etiologic factors have been described, which has facilitated the development of more effective therapeutic approaches.

However, many peculiarities of KS still remain unsolved, and thus more detailed studies are needed. Of special importance seems the endemic type of KS since it already is the most common neoplasm in certain parts of Africa and its prevalence is still growing.

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