Kaposi's multiple hemorrhagic sarcomatosis*
*Sarcomatose múltipla hemorrágica de Kaposi**

Silvio Alencar Marques[1]

Under this title, 80 years ago, on the first issue of the *Annaes Brasileiros de Dermatologia e Syphilographia*,[1] professor Armínio Fraga, at that time full professor at Brazil Medical School, today Federal University of Rio de Janeiro - UFRJ, and head of the Venereal and Skin Diseases Health Center at the Holy Mercy Hospital of Rio de Janeiro, described a clinical case, reproduced its image and wrote about Kaposi's Sarcoma (KS) (Figure 1).[1] He referred to the 56 year-old patient as follows:

"Invited by Dr. Eurico Villela, we examined the patient, who presented a large number of nodules, some superficial, salient and pedunculated, others intradermal, firm in consistency, of various sizes, unpainful, non-ulcerated appearing either over infiltrated surfaces, or over healthy skin" (Figure 2).

And, when discussing the case:

"Concerning etiology, traumatism, constant irritation and certain predisposing factors are known to have some importance, but the main cause is still ignored. The majority of cases has been observed in adult males. Duration of the disease is long, ranging between 2 and 20 years, and its end is always a fatal one. Treatment of identical cases with arsenicals has yielded non-appreciable outcomes. In the hands of a few observers, MacKee, Remer, among others, above all in not very extensive cases, X-rays and radium have yielded good results."

At that time, nothing would give a clue about the true clinical, epidemiological and etiological revolution this infirmity would undergo, since today it is considered not as a true cancer or malignancy, but as a virus-induced cell proliferation, receiving thus the denomination of "Kaposi's disease".[2]

The beginning of this saga was in 1872, when, under the title of *Idiopathisches multiples Pigmentsarkom der Haut*, Moritz Kaposi (1837-1902) described five cases, all in men over forty years of age, who presented erythematous-violet nodules in the lower limbs.[3] From some of these cases he obtained material for pathological studies, which he shared and discussed with Rudolf Virchow (1821-1902). In this pioneering publication, Kaposi did not reproduce clinical or histopathological images, which would only appear in the *Atlas der Hautkrankheiten*, edited by Hebra, Elfinger e Heitzman in 1876, apud Gottlieb & Ackerman (1988).[4] In 1894, in a new publication, Kaposi used the name *Sarcoma idiopathicum multiplex haemorrhagicum*, so as to avoid confusions with melanoma.[5] The eponym Kaposi´s Sarcoma came up only in 1912, as proposed by Sternberg.[6] In the end of the 19th century and in the first decades of the 20th century, several reports succeed, suggesting that this illness was more prevailing in patients of Jewish Ashkenasi origin and patients from Mediterranean and East Europe, being particularly rare in children and adolescents.[4] At that time, determination of the tumor-originated cell was highly controversial. Many authors chose a vascular endothelium origin, whereas others preferred an origin at perivascular lymphatic or even reticuloendothelial system.[7] Such controversy endured until recently, when immunohistochemical techniques confirmed cell origin at the vascular endothelium.[8] The clinical concepts of the disease being essentially sporadic, indolent and associated to Europeans and descendants were abolished in the 1960s, with a report of a series of cases observed in large numbers in Africa and with an aggressive clinical presentation, diverging from the classic form. This second clinical presentation, in an endemic form in Central and Equatorial Africa, particularly in the Congo, Uganda, Tanzania and Rwanda,[9,10] corresponded to a variable proportion going from 1 up to 12% of diagnosed cancers in those regions.[9,11] This novel clinical form, either locally or systemically aggressive, with gastrointestinal and pulmonary dissemination, and a specific childhood lymphadenopathic variant, widened the disease's clinical spectrum known at the time. Nevertheless, histological identity and a predominance in adult males and lower limbs maintained the connection between the endemic and classical forms of Kaposi's Sarcoma. A new addition to KS

Received on September 05, 2005.
Approved by the Editorial Council and accepted for publication on September 05, 2005.
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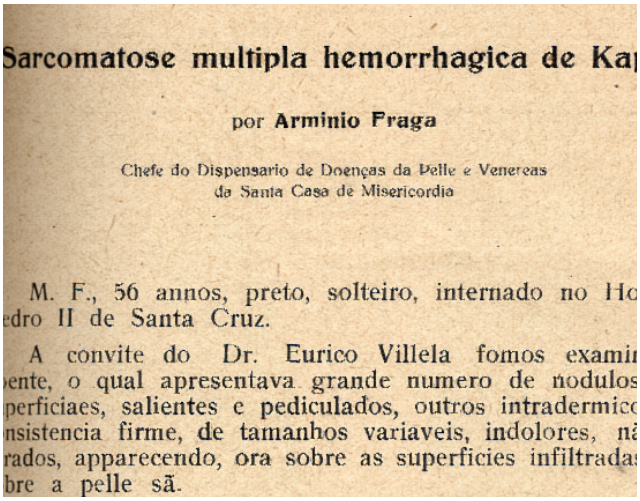

Sarcomatose multipla hemorrhagica de Ka

por Arminio Fraga

Chefe do Dispensario de Doenças da Pelle e Venereas da Santa Casa de Misericordia

M. F., 56 annos, preto, solteiro, internado no Ho
edro II de Santa Cruz.

A convite do Dr. Eurico Villela fomos examin
ente, o qual apresentava grande numero de nodulos
perficiaes, salientes e pediculados, outros intradermic
nsistencia firme, de tamanhos variaveis, indolores, nã
rados, apparecendo, ora sobre as superficies infiltrada
bre a pelle sã.

Figure 1: Reproduction of the first page of Arminio Fraga's paper

Figure 2: Reproduction of a Kaposi's sarcoma belonging to the case described on Volume 1 of the *Annaes Brasileiros de Dermatologia e Syphilographia*

epidemiology occurred in the 70s, when increased frequency of Kaposi's sarcoma was reported in post-transplantation immunocompromised patients or in those bearing autoimmune disorders[14] added to the increased frequency of the disease following existence of primary cancers, particularly those of lymphatic-reticular origin.[12,13] This association, more common among patients with renal transplants, generally after a long period of immunosuppression with azatiprine and glucocorticoid or cyclosporin, was characterized by a less indolent evolution and remission or clinical improvement following reduction of immunosupressing therapy. From the first reports, possible facilitating mechanisms for the increased occurrence of cancers in immunocompromised patients had been speculated, not only for Kaposi's Sarcoma, but also decrease in immune surveillance, iatrogenically induced, chronic antigenic stimulus by the foreign transplanted tissue or virus-induced oncogenesis. Kaposi's Sarcoma incidence in transplanted patients was considered to be from 500 to 1000 times more often than expected for general population, its occurrence was predicted in one to 4% of post-transplantation patients.[11,15] This etiopathogenic connection to immunomodulators can even be associated to local use, which has been demonstrated by a report of specific lesion in sites were local tacrolimus was being used.[16]

The great epidemiological transformation in the history of Kaposi's Sarcoma, however, was derived from the intuition and perception of dermatologists and pathologists then associated to the Laboratory of Dermatopahology at New York University, who were able to diagnose, seek information and recognize being faced with a new clinical-epidemiological addition to then sporadic profile of Kaposi's Sarcoma. These observations were published in a rapid sucession in 1981.[17-19] Still in those years, dozens of cases were diagnosed in the United States of America, as an 'epidemics', which, together with the simultaneity of diagnoses of opportunistic infection in young adults, particularly by *Pneumocystis carinii*, provided the conceptual basis to what would be later called Acquired Immunodeficiency Syndrome (AIDS).[4] In the following years, yet preceding highly active anti-retroviral therapy (HAART), Kaposi's Sarcoma, now an epidemics, showed itself as an aggressive, quickly progressing disease, frequently specific cause of death in AIDS patients (Figure 3). The main victims of this clinical form of KS were those with epidemiology of homosexual transmission of the Human Immunodeficiency Virus (HIV). The incidence of KS in this group reached 40% in the beginning of AIDS epidemics, depending on the type of sexual practices and with a relative risk of developing it going up to 20 times greater, when compared to patients of other risk groups for HIV infection.[20-22] This differentiated incidence profile suggested, among other co-factors, an imputable etiopathogenic role to a sexually transmitted, but not bloodborne agent. Cytomegalovirus (CMV) was considered as a strong possibility owing to the frequency of co-infection among homosexuals. This notwithstanding, a significant non-dectection of serologic positivity for CMV in patients with classic, endemic or iatrogenic forms of Kaposis's Sarcoma, and the non-detection of CMV viral genome in sarcomatous cells weakened such possibility.[21,22] The same happened with theories of associations to other viral agents then known, such as Hepatitis B Virus, Hepatitis C Virus, type II Herpes Virus *hominis* and HIV itself.[21,22]

In 1994, a decisive scientific finding concerning etiology was made when Chang et al.[23] identified a herpes virus-like DNA sequence in a Kaposi's Sarcoma tissue associated to AIDS. In this investigation, a certain sequen-

ce was detected in 90% of the tissue obtained from KS lesions of AIDS patients, in 15% of non-KS tissues of the same patients, but it was not detected in healthy tissues taken from control non-AIDS patients. The sequences were considered to be homologous, albeit distinct from viral genes present in Epstein-Barr, *Gamaherpersvirinae* and *Herpesvirus saimiri* viruses, and were concluded to correspond to a new human herpes vírus, called Kaposi's sarcoma associated herpes vírus (KSHV), later type 8 human herpes virus (HHV-8). These data were corroborated in 1995 by Moore and Chang,[24] who analyzed DNA sequences from samples of KS lesions associated to AIDS (epidemics), classic KS, KS of HIV-seronegative homosexual patients, samples from healthy tissues of the above-mentioned patients and samples form control healthy individuals. Reference sequence was detected in 10 out of 11 samples of AIDS-associated KS, all 6 samples of classic KS, all four samples from HIV-negative KS patients, 3 of 14 samples of non-compromised tissues from AIDS-associated KS patients and in a single sample out of 21 from control patients. These data significantly reinforced the association of the sequence, thus consolidating the premise of the same causal agent in the different types of Kaposi's Sarcoma. Subsequently the very same herpes virus-like sequences were detected in different investigations, definitely associating the novel agent (HHV-8) as etiologic agent of the different subtypes of KS.[25,26] HHV-8 is a DNA virus of the herpesviridae family, *Gamaherpesvirinae* subfamily and *Rhadinovirus* genus.[2,11] *Alphaherpesvirinae* subfamily subtends human herpes simplex (HHV-1 and HHV-2) and varicella virus (HHV-3); *Betaherpesvirinae* subfamily includes CMV (HHV-5) and *Roseolovirus* (HHV-6 and HHV-7); and *Gamaherpesvirinae* subfamily, besides HHV-8, includes Epstein-Barr virus (HHV-4). Herpes viruses can exist in a latent phase with host cell nucleus, which can be activated, for instance, by ultraviolet radiation or immunosuppression, to lytic phase, resulting in cellular damage and expressing through different clinical pictures. Association to cancers and cellular proliferation is a peculiarity of HHV-4 (Epstein-Barr) and HHV-8.[2] HHV-8 correlates not only to Kaposi's Sarcoma, but also to a rare subtype of lymphoma, named primary effusion lymphoma, and to Castleman's disease.[2] HHV-8 has five subtypes, named by letters A to E, based on genetic variability concentrated on open reading frame K1 (ORF-K1), with distribution bound to geographical location and ethnic group, and subtype B, considered as the original one, is more prevailing in Africa.[2,27] 27 In Europe and USA subtype A prevails; subtype D in Asia and Australia and subtype E in indigenous population in Brazilian and Equatorian Amazon.[27] In São Paulo, patients with KS associated to AIDS, HHV-8 subtype A was predominant (48%), followed by subtypes c (30%) and B (21%), with a statistically significant association between homosexual and bisexual practices as risk factors for HIV, and subtype A.[27] The oncogenic role of DNA viruses is complex, and the premises for such are twofold; the virus must be integrated to the genome of the host cell, thus inducing alteration in the cell geneic expression. This alteration can be due to a combination of various viral oncogenes or tumor suppressing genes, with different promoters or yet expression hybrid proteins with oncogenic potential.[2] The virus integrated to the cell genome is also supposed to be in a latent state, with no cell death because of lytic action, which allows a continuous expressions of oncogenes or a decreases expression of tumor suppressing genes.[2] A co-factor of the high frequency of KS in AIDS patients may be a result of a synergistic action of HIV and HHV-8 through protein Tat, which possesses the capacity to activate β-FGF (β-fibroblast growth factor), with a potent angiogenic action.[27] The potential of HHV-8 activation that is exerted by HIV augments the viral load of HHV-8 and the expression of potential oncogenes, synthesis of VEGF (vascular endothelial growth factor), anti-apoptosis gene and a gene antagonizing interferon-mediated antiviral immunity.[28] Numerous sero-epidemiological studies have demonstrated a strong positive correlation between HHV-8 and population under risk of KS.[2,11] Specifically in the state of São Paulo, seropositivity has been demonstrated to oscillate between 1 and 4.1%, among children and healthy young adults; up to 32.6% in HIV-bearing patients with no evidence of a Kaposi's Sarcoma diagnosis; and up to 98.7% in HIV patients with Kaposi's sarcoma.[29] In patients who develop post-transplantation KS, seropositivity to HHV-8 is pre-existing in most of the cases, but acquiring the virus is also possible through infected donated tissue.[11]

From a therapeutical standpoint, to radiation

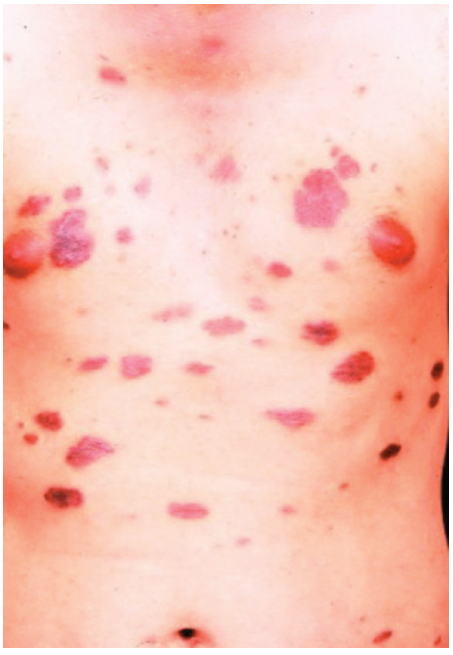

Figure 3: Kaposis's Sarcoma associated to HIV infection. Multiple erythematous-violet plaques in the trunk

therapy, already known in Armínio Fraga's times,[1] added up chemotherapy and therapy with alpha-interferon, promising for classical forms of Kaposis's Sarcoma,[21,22] whereas in KSs associated to HIV infection, highly active anti-retroviral therapy (HAART) has a major role in the reduction of incidence and alteration of clinical course in those already bearing KS at begging of antiretroviral treatment, with a decrease or even disappearing of HHV-8 detection.[30]

Thus, 80 years past the clinical observation of a patient with Kaposi's Sarcoma, published by Professor Armínio Fraga, the present article seeks to demonstrate the incredible dynamics of both Biology and Medicine, and serves as an inspiration to the study of the molecular bases of virus-correlated and immunosuppression-dependent diseases, for the understanding and the possibility of innovating therapeutical propositions have a basis there. ❑

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