Kaposi's Sarcoma – visceral involvement in AIDS patients

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Abstract

Kaposi's sarcoma (KS) is a multifocal neoplasm that affects mainly the skin, but it can also affect the visceral organs. Four variants are described: classic, African endemic, iatrogenic and epidemic KS. The latter variant emerged after the association of this tumor with AIDS, when it took on important proportions, both in terms of frequency and in its widespread clinical expression, with marked visceral involvement. Homosexual men are the most affected risk group, and there are various etiological hypotheses for this neoplasm. There is a correlation between the level of immunological deficiency and the extent of the disease.

AIDS-related KS presents visceral involvement in 50 to 70% of patients. However, isolated visceral involvement is rare. Gastrointestinal, pulmonary and cardiac involvement in the disease are often described, as these are the most frequently affected organs.

Treatment is merely palliative and can be local or systemic. KS itself is rarely the cause of death, except for cases with pulmonary involvement, in which the patient normally dies from opportunistic infections.

Keywords: Kaposi's sarcoma; visceral KS, HIV infection, acquired immunodeficiency syndrome (AIDS).

Introduction

Kaposi's sarcoma (KS) is a neoplasm of multifocal origin, characterized by purple- or blue-brownish spots, plaques or nodules affecting the skin or other visceral organs.[1]

This tumor was first described in 1872 by Moritz-Kaposi as idiopathic multiple pigmented skin sarcoma.[1,2,3] Since then, despite its rarity, several variants of KS have identified, namely; classic, African endemic, and iatrogenic KS, the latter being associated with the immunosuppressant treatment of patients who have undergone organ transplant.[2,3,4]

In 1981, a worsening of this pathology was verified, associated with the emergence of AIDS,[5,6] and the existence of a fourth variant began to be considered: epidemic KS, in which visceral involvement is frequent. [2,3]

Table 1 shows the main epistemological and clinical characteristics of the Kaposi's sarcoma variants.[1]

Incidence

The classic variant of KS is very rare, with an incidence of between 0.02 and 0.06/100,000/year;[7] meanwhile, the African endemic variant represents about 10% of neoplasms in the Congo, Kenya and Zaire.[3] Patients who have undergone organ transplant and immunosuppressant therapy, particularly with Cyclosporin A, may present secondary neoplasms.[3]

Of these, 3.4% are KS and emerge, on average, 16.5% months after transplant, usually receding with the suspension of the immunosuppressant drug.[2]

At the beginning of the AIDS epidemic, KS was the first manifestation in 25 to 30% of cases, and this number has now reduced to approximately 15%.[3] Its incidence varies according to the risk group, and is as high as 40% among homosexuals,[8] but only 1% among hemophilic patients. It is also more frequent in women who have contact with bisexuals.[2]

There is a predominance among Caucasian males, the average age of onset is 38 years old, and a greater incidence is observed in the United States and Europe.[1,9]

Etiology

The etiology of Kaposi's sarcoma is unknown, but it is thought that it may be multifactorial.[1]

Given the frequent appearance of this pathology in groups of patients with marked promiscuity, the

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TABLE I

Variants of Kaposi's Sarcoma

	Population	Age	Clinical manifestations	Evolution	Sex M/F
Classic	Jew, Mediterranean	50-80	Lower extremities, with venous stasis and lymphoedema; skin and late visceral dissemination	Indolent	10-15:1
Endemic	African adults	25-40	Localized nodular lesions; large exophytic tumors; bone invasion	Indolent	17:1
	African Children	2-13	Generalized lymphoedema	Fast/ progressive (2-3 years)	3:1
Iatrogenic	Immunosuppressed, transplanted	20-60	Skin localized or diffused	Indolent or fast/ progressive; can recede	2,3:1
Epidemic	AIDS, homosexual	18-65	Diffuse mucocutaneous lesions; frequent involvement of ganglia and deep organs (GI, lung)	Fulminant	106:1

hypothesis of its association with sexually transmitted diseases has been proposed, with the involvement of infectious agents such as CMV, papillomavirus-16, herpes and hepatitis A and B viruses, or an unknown microorganism transmitted via the feces.[2,10,11] It is believed that HIV itself may be directly or indirectly responsible for the onset of KS.[2] Cell growth factors may also be involved, as in the case of the factor induced by the tal-1 gene of HIV, interleukin-6 (IL-6), oncostatin M and the fibroblast growth factor (FGF-6).[1,3,5,12]

The KS can be dependent on environmental factors, such as repeated antigenic stimulation, or even factors related to lifestyle.[1,10,11]

The association of this neoplasm with HLA-DR% suggests the existence of a genetic predisposition for its emergence.[1,5,7]

Finally, KS appears to be associated with various diseases, such as neoplasms of the lymph-reticular system, plasma cell dyscrasias, thymoma, polymyositis, BSLE, pemphigus vulgaris and temporal arteritis.[1,5]

Histopathology

The probable origin of KS cells is the mesenquimatous cells of the vascular or lymphatic endothelium.[1,3,8]

Its characteristic histological appearance includes the existence of bundles of spindle cells intertwined with the vascular structures, forming a network of reticular and collagen fibers; red blood cells overflowing through slits to peripheral blood and lymphatic vessels; and deposits of hemosiderin between the spindle cells.[1,3]

Three histological types are described: the mixed cell pattern, with proportions identical to that of spindle cells, vascular and capillary slits; the mononuclear pattern, with proliferation of one cell type only (generally spindle cells); and the anaplastic form, with marked cell pleomorphism and innumerous mitosis.[4]

Staging

Classification of AIDS-related epidemic KS, in terms of staging, is important to guide the therapy, due to its frequent progression to diffuse neoplasm. Thus, an initial or low-risk stage can be considered in which the disease is localized, reaching the mucocutaneous or ganglion regions; and an advanced or high-risk stage, characterized by extensive or diffuse lesions and visceral involvement (*Table 2*).[2]

The factors for a good prognosis are an initial stage, absence of opportunistic infections, absence of systemic symptoms (fever, anorexia, weight loss), CD4>200/ mm^3, CD4/CD8>0.5, absence of endogenous serum interferon activity, high proliferative response to E. coli and absence of severe anemia (HB> 10g/ dl).[4, 11]

The presence of visceral lesions is associated with a shorter survival, though death is generally caused by opportunistic infections.[8] Progression of the disease

TABLE II

AIDS-related KS Staging

	High risk (1)	Low risk (0)
Tumor (T)	Edema and ulceration associated with tumor; extensive oral KS; GI KS; other non-lymphatic organ KS	Restricted to skin and/ or lymphatic ganglia and/ or minimal oral disease
Immune system (I)	**CD4< 200**	**CD4> 200**
Systemic disease (S)	History of opportunistic infection and/ or oral candidiasis, B symptoms; Karnofsky index <70; other HIV-related diseases (e.g. neurologic disease, lymphoma)	No history of opportunistic infection or oral candidiasis, no B symptoms; Karnofsky index >70.

can also occur in association with pneumocystosis or corticotherapy.[2]

Clinical symptoms

Classic KS is a predominantly cutaneous disease involving the lower limbs, with rare ganglion or visceral lesions.[2,3] The African endemic variant can present four different clinical patterns: nodular benign skin lesions, similar those of the classic variant, aggressive localized skin disease involving the soft tissues and bones, mucocutaneous and florid visceral disease, and lymphadenopathic disease.[1,2] The iatrogenic variant is primarily a skin complication of the immunosuppressant therapy.[2]

AIDS-related KS, in turn, is characterized by a wide clinical spectrum that overlaps with the characteristics of other variants.[2]

Mucocutaneous involvement is usually multifocal and bilateral,[2,8] with emergence of red or violaceous spots, papules or nodules that progress and coalesce, forming large tumors and ulcerated plaques.[1] The oral cavity is involved in 22% of cases, and of these, 50% are located in the palate.[2] Ocular lesions can be observed in 20% of patients, also with frequent involvement of the nose, retroauricular region, trunk, penis and lower limbs.[2]

Lymphadenopathy impairment occurs in about 50% of cases, and may be responsible for the emergence of edema or alterations in the pattern of skin lesion.[2]

Visceral involvement of AIDS-related KS, despite its frequency (50-70% of patients), is generally asymptomatic.[2] The gastrointestinal apparatus is involved in 50% of cases:[7,8] 24% in the gastroduodenal region, 12% in the colon, and 15% in the upper and lower gastrointestinal regions.[13] The lungs and heart present lesions in about 20% of patients.[14,15] Although these organs are the most commonly affected, KS can affect almost any structure, such as the liver, pancreas, spleen, adrenals, larynx, thymus, bone, diaphragm, retro-peritoneum, urogenital apparatus and brain.[2]

In patients with epidemic KS, involvement of the gastrointestinal apparatus, lung and lymphatic ganglia was observed in 90% of cases.[16] However, the existence of visceral KS without concomitant skin lesion was observed in just 5% of patients.[17]

Occasionally, atypical forms of presentation can occur, which are difficult to diagnose, such as persistent fever,[18] probably paraneoplastic, and deep gangliar or isolated hepatic locations, involvement of the digestive system with exudative enteropathy, and sepsis due to perforation of intestinal lesions.[9]

Gastrointestinal expression

Gastrointestinal lesions are generally asymptomatic,[8,9] however, a digestive syndrome can occur, with diarrhea, abdominal pain, anorexia and weight loss.[6,9] Less frequently, digestive hemorrhage and intestinal obstruction occur.[19] When these symptoms are present, the differential diagnosis is reached from opportunistic infections such as CMV colitis, cryptosporidiosis, Isospora belli protozoan and MAI infection.[6,20]

The most commonly observed endoscopic appearance of KS is the presence of polypoid plurinodular tumors.[19] These may be in the form of a single tumor or a diffuse micropolypoid form.[19]

However, only 30% of biopsies make diagnosis possible, due to the submucosal location of lesions.[9]

Lung expression

Respiratory symptoms are generally present in bronchopulmonary KS, such as non-productive

TABLE III

Lung scintigraphy with Gallium and Thallium (differential diagnosis of AIDS-related pulmonary KS)

	Gallium	Thallium
Pneumocystosis, Tuberculosis, MAI Lymphoma	Positive, diffuse Positive focal Positive	Negative Negative Positive
Kaposi's Sarcoma	Negative	Positive

cough, dyspnea, and fever. Less frequently chest pain and hemoptysis, are also characteristic of most opportunistic infections involving the lungs in AIDS patients.[6,21,22,23,24,25] Thus, before attributing the complaints to KS, pneumocystosis, Legionella infection, CVM pneumonitis and tuberculosis should first be excluded.[6] Such differential diagnosis is more difficult as it can happen a concomitant opportunistic infection in 50% of cases with pulmonary KS. [24]

This neoplasm may involve the tracheobronchial tree, the pulmonary parenchyma, the mediastinal ganglia and the visceral pleura.[21, 22] Lesions of the palate are frequently found in the association with pulmonary disease.[23]

Pulmonary KS is, in most cases, diagnosed after death, due to the difficulty of its diagnosis in the patient alive.[23,25,26] The clinical and radiologic aspects are not very specific and the endobronchial lesions are submucosal and sometimes non-existent, and diagnosis is made through direct visualization in 73% of cases and through biopsy in 60%.[21,22] Parenchymal lesions are focal, therefore transbronchial lung biopsy is only diagnosed in 26% of cases, while lung biopsy via thoracotomy is positive in only 18% of patients.[21,22,26]

The anatomical-pathological aspects observed are identical to those of the other locations, with tracheobronchial, pleural or pre-bronchial or perivascular parenchymal erythematous or violaceous plaques.[25]

The presence of hidden alveolar hemorrhage, characterized by a number of macrophages with hemosiderin higher than 30% in the bronchoalveolar lavage, is also suggestive of KS.[22, 25, 27]

Concerning functional respiratory tests, normally a restrictive spirometry pattern is found, with possible obstructive pattern in the presence of voluminous endobronchial lesions. [21] A reduction in O_2 diffusion capacity is also verified, as well as a reduction in alveoloarterial O_2 gradient with physical exercise, unlike pneumocystosis, where the gradient is increased.[21, 28]

The radiological aspects most commonly observed are linear interstitial opacities, predominantly perihilar, angio- and bronchial-centered opacities (57-83%), poorly-defined opacities, coalescent with subpleural peripheral topography (15-33%), unilateral or bilateral pleural effusion, and mediastinal or hilar adenopathies (20-50%).[14,23,24] These images, despite being suggestive of KS, can appear in a variety of other AIDS-related pathologies, and scintigraphy can help form a differential diagnosis.[5] Pulmonary KS is the only disease which presents absence of gallium caption and thallium fixation (the lymphoma is positive in both radionuclides).[5] Scintigraphy with thallium should be carried out only about three hours after injection, to eliminate false-positive results due to lung edema or congestion associated with the infections (*Table 3*).

The average survival time, from diagnosis of pulmonary KS, is approximately eight months.[21] The existence of lung involvement by the sarcoma is not correlated with the length or extent of the mucocutaneous or ganglion disease.[25] Prognosis seems to be worse when there is concomitant pleural effusion.[29] Despite all this, pulmonary KS is the direct cause of death in only 27% of cases,[23] due to obstruction of the upper airways, intra-alveolar hemorrhage or parenchymal destruction.[16,21,25]

Cardiac involvement

Pericarditis, with or without tamponade, is the most frequent initial cardiac alteration in AIDS, and KS is one of the possible etiologies.[30,31] Other hypotheses to be considered are infections with Staphylococcus aureus, Actinomycetes (Nocardia), Herpes simplex, Cryptococcus neoformans, tuberculosis, MAI and lymphomas.[30,31,32,33]

The KS affects the heart in 20% of cases, with visceral and parietal pericardial involvement and, though less frequent, myocardial involvement.[31,32,33] There is a predilection for the epicardium and the subepicardial fat, and the coronary artery adventitial and the large vessels may be involved.[30,31,31,34] It is generally asymptomatic and associated with the disseminated disease. However, there may be involvement of the right atrium, with symptomology,[33] or it may be

TABLE IV

Therapy of epidemic Kaposi's Sarcoma

Local
- Make-up
- Local excision
- Cryotherapy with liquid nitrogen
- Laser photocoagulation
- Local radiotherapy
- Local injection of vinblastine, vincristine or alpha-interpheron

Systemic
- Alpha-interpheron
- Simple or combined chemotherapy, bleomycin, vinblastine, vincristine, cyclosphamide, etoposide, doxorubicin

Experimental
- Liposomal chemotherapy
- Angiostatic compounds

accompanied by fibrinous periocarditis.[34] Two cases with cardiac tamponade are described.[17,31,32,33]

Therapy

In general, patients with classic KS present good response to local therapy. The African endemic variant, except in cases of lymphadenopathy, shows good response to systemic treatment and the iatrogenic variant recedes with suspension of the immunosuppressant drug.[2]

In relation to AIDS-related KS, not only there is no curative therapy available, but also the local or systemic treatments used seem to fail to extend the survival time of patients and there is no proof of any advantages of concomitant use of zidovudine (AZT).[12] Thus, the main objective of epidemic KS treatment is palliative. The therapy is indicated, in particularly, for cosmetic control of disfiguring lesions, reduction of voluminous lesions or lesions causing functional alterations, pain or edema, associated with lymphadenopathy, and for the relief of symptomatic systemic disease (*Table 4*)[5].

Radiotherapy, besides its use in localized, painful skin lesions, or skin lesions with functional alteration (for example, oral, plantar, anorectal and genital lesions), can be used in cases of lung involvement which is refractory to chemotherapy and where the goal is fast relief of symptoms.[24,35]

When administered in high doses, recombinant interpheron alpha-2a, an immunoregulatory and antiproliferative substance with antiviral action, can result in regression of the tumor in 20-40% of cases.[11] This treatment is indicated when the patient's immune state is still relatively preserved, i.e., CD4>200/mm^3, absence of systemic symptoms and symptoms of opportunistic infections, and preserved skin reactivity.[8, 9, 36]

The main indication of systemic chemotherapy is to reduce morbidity associated with extensive disease.[11] A sole agent or a multiple combined therapy may be used.[37] The latter seems to offer better results, although the risk of myelosuppression is increased.[11] Thus, with the commonly used ABV scheme (adriamycin, bleomycin and vincristine/ vinblastine), it is possible to achieve 88% remission, 38% of which are cases of full remission.[11] Unfortunately, recurrence is the rule, occurring two to three months after interruption of treatment, and the average survival time is about nine months.[11] Most patients die due to infectious complications (66%). In 14%, death is due to extensive KS associated with infections or cachexy, and in 4% of cases, it results from extensive lung involvement.[9,11]

Some promising therapies, still in the trial phase, include drugs with angiogenic action, such as recombinant human platelet factor 4, fumagillin analogs or synthetics, synthetic substitutes of heparin, vitamin D3 analogs, compounds of the bacterial wall cell, and inhibitors of cytokine stimulants and/or receptors of specific cytokines of KS cells.[2]

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