HIV infection associated with pulmonary Kaposi´s sarcoma

Eugénio Teófilo,* Pedro Figueiredo**

Abstract

The recent emergence of the Kaposi Sarcoma (KS) epidemic, in current clinical practice, will result in rare clinical entities being more frequently found e.g. Pulmonary Kaposi´s Sarcoma (PKS). Radiology has an important role to play in the evaluation of PKS scope. PKS aggressive expression has lead to the development of new treatments in a number of different areas (immunoregulatory, hormonal and cytostatic). The new concepts about the probable origin of the disease might enable a prophylactic treatment for the immunodepressed infected with the AIDS virus.

Key words: human herpes virus 8, cytokines, oncogenesis, imageology, polychemotherapy.

Introduction

The initial description by Moritz Kaposi made reference to an indolent form of cutaneous neoplasm affecting elderly man. Subsequent identification of the African endemic form of this tumor in iatrogenic immunosuppressed patients has fuelled a great speculation regarding its origin.

The emergence, almost two decades ago, of an HIV infection pandemic has coincided with the emergence of a more aggressive clinical form, often involving other organs, causing considerable morbidity and mortality.[1]

Recent data regarding Kaposi´s sarcoma etiopathogenesis and the new available therapies may enable an improvement of what is so far a dark prognosis for the pulmonary form of such pathology.

Epidemiology and pathophysiology

Four forms of Kaposi´s sarcoma are described, and then in order of appearance, can be classified in: classic, endemic, associated to immunosuppressing therapy and, lastly, the epidemic (*Table 1*). In all KS forms (excepted in those associated to immunosuppressing therapy) there is a marked predominance of the male gender. The affected populations in the first three forms led to the suspicion that hormonal factors, age and immunosuppression were important in the disease pathogenesis.

The classic form happens predominantly in elderly men, the endemic in young men apparently healthy (but also in children)[2] and associated to immunosuppressing therapy was seen initially in patients subject to kidney transplant, but it has also been observed in other diseases in need of immunosuppressing therapy, being recorded for the first time the withdrawal of such therapy.[3,4]

The epidemic form, associated to HIV, has emerged initially in homosexual men, being then raised the hypothesis that some recreational drugs (namely amyl nitrate) could be involved. The epidemiological analysis has led rapidly to the hypothesis of an infectious agent conveyed sexually and due to the immunosuppression induced by HIV, would lead to KS. [5-14]

In 1994, Chang et al. have isolated for the first time, DNA sequences in KS lesions of a new gamma-herpes virus, totally sequencing in the meantime, the human herpes virus 8 (HHV8).[15] This virus contains genes of products potentially important in oncogenesis as D cyclyne homologous, bcl2 and interleukin 6 (IL6); it is lymphotrophic and apart of KS it was associated to multicentre Castleman's disease and cavity lymphomas (at present called primary effusion lymphomas).[16-26]

Several authors have isolated HHV8 in the blood, sperm, saliva and prostatic secretions,[26-33] and prospective studies of some cohorts [34,35] have demonstrated that a previous infection with HHV8 was related with the subsequent incidence increase of KS (both in seropositive as in seronegative for HIV).[36]

*Resident to the Internal Medicine Supplementary Internship

** Radiology Hospital Assistant

Santo Antonio Capuchos Hospital, Lisbon

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TABLE I

Clinic forms of Kaposi's Sarcoma: Epidemiology

	Age and gender	Associated virus	Visceral attainment	Evolution
Classic	Elderly men	HHV8	Rare	Indolent
Endemic	Young men	HHV8	Variable	Variable
Iatrogenic immunosuppression	Variable elderly	HHV8	Rare	Indolent
Epidemic	Young men	HHV8 and HIV	Common	Rapid

The current pathophysiologic model supports that KS associated with AIDS emerges through HIV direct and indirect action in a previously infected with HHV8, changing this way the natural evolution of such disease.[37]

The direct action is due to the product activity of the tat gene (TAT protein) inducing the proliferation of KS fusiform cells and IL6 production[38,39] (IL6 has autocrine action in KS cells) and it is linked to integrin receptors (important molecules of cellular adhesion). HIV indirect action is related with a decrease of immunologic surveillance that a decrease on $CD4^+$ brings with it, and with a deregulation of the cytokines pattern induced by HIV, with an increase on IL1, TNFa, IL6 and growth factors as bFGF (basic fibroblast growth factor).[40]

In summary, HHV8 infection is the starting stage which transforms the cells making them sensitive to TAT protein actions, and to high cytokines in HIV infection (IL1, IL6 and bFGF). These cells initial expansion would be oligoclonal, but subsequent mutations would lead to monoclonal expansion.[41]

Clinical aspects

KS occurs in different degrees of immunosuppression in the HIV infection (*Table 2*), being however a diagnosis criteria in AIDS.

The endemic form (or African) shows different morphologic types, more or less homogenous, with a distinct biologic behaviour, what enabled its subdivision in nodular, florid, infiltrative and lymphadenopathy (*Table 3*).

Several staging systems have been made, being the classification used at present the same as AIDS Clinical Trial Group (ACTG), which includes tumoral mass, immunologic condition and concomitant/previous systemic disease (*Table 4*).

At present, there is a change proposal for CD4+ value of 200 to lower than 150, as a high risk marker [42] (to better reflect the cleavage between a good and bad prognosis).

The visceral involvement is a bad prognosis factor and when reaching the lung has a particularly bad prognosis. The frequency that lungs are affected changes according to different series from 6 to 32%. The assessment of such series has enabled to identify also other bad prognosis markers related more closely with the pulmonary form, as anemia and hypoxemia. The survival of this patient's group with KS is below one year.[43,44]

The diagnosis of pulmonary involvement[45] can be very difficult (only necropsis), as perhaps there are no cutaneous lesions and the patient may be asymptomatic. Most patients, however, present fever, cough, asthenia and dyspnea which can easily be mistaken with symptoms of an opportunistic infection (pneumocystosis and tuberculosis). Imageology has given an important contribution to the diagnosis suspicion through high resolution CT scan and NMR (see radiology aspects). The bronchofiberscope enables to visualize endobronchial images,[46-47] but in cases where the infiltration is only in the parenchyma, the fluid returning from BAL positive cells for CD34 marker should be identified, or to carry out the HHV8 detection, being this positive in patients with pulmonary KS and even in patients that initially had no evidence of pulmonary involvement but who would present it at a later stage.[48-50]

Another available technique in this situation is to perform a serial lung scintigraphy (with galium[67] and thalium[201] and the result is the non-absorption of gallium, a strong thallium absorption, the opposite of the infectious pathology).[51]

Often the pulmonary expression is followed by pleural attainment, with serum-hematic pleural effusion or frankly hematic, where $CD34^+$ cells can be detected. [52]

TABLE II

HIV Infection Staging

Laboratorial C.	Clinical Categories		
CD4+	(A) Acute, asymptomatic or LPG infection	(B) Symptomatic not included in (A) or (C)	(C) Situations indicating AIDS
(1) > 500 /µL	A1	B1	
(2) 200-499 /µL	A2	B2	
(3) < 200 /µL			

(In the USA; all shady areas correspond to categories defining AIDS; in Europe only the darkest areas correspond to such definition)

TABLE III

Clinical presentation of the endemic form

	Age/Gender	Morphology	Structures	Evolution
Nodular	Men Young adults	Skin Plaque/Node	Skin	Indolent
Vegetative	Men Young adults	Skin Vegetative Mass	Reaching the bone frequent/	Quick local
Infiltrative	Men Young adults	Large plaques	Reaching the bone almost always	Quick local
Ganglionar	Youngsters Children	Generalized adenopathies w/skin lesion	Organ involvement	Quick (death in 3 years)

Radiologic aspects

Changes in the thorax radiogram reflect the cellular origin of the Pulmonary Kaposi's Sarcoma (PKS): the tumoral fusiform cells develop themselves from pluripotent cells or endothelial cells,[53] proliferating in the pulmonary interstice with perilymphatic distribution, i.e., in the peribronchovascular axial interstitium.[53] Therefore, PKS produces in the thorax radiogram bilateral linear opacities predominantly perihilar (*Fig. 1*), that in CT scans are translated by irregular thickening of peribronchovascular sheaths and thickening of bronchial walls (*Fig. 2*).[53-57] The involvement of the peripheral interstitium by tumoral growth or by the resulting edema of central lymphatic obstruction, produces Kerley B lines in pulmonary basis, representing a thickening of the interlobular septa.[53,56,57] With the tumoral growth can emerge a consolidation also a perihilar distribution, representing a confluent tumor.[53]

PKS is characterized by the presence of poorly defined nodules, multiple and bilateral, with different dimensions (0.5 – 3 cm), [53-57] representing tumoral proliferation stretching to the lung parenchyma.[53] When these nodules are present, there are invariably perihilar opacities. [53]

From 16 to 63% of PKS patients present hilar or mediastinal adenopathies,[53,54,56,57] always associated to parenchymal changes (*Fig. 3*).[57] Of note, however, the hilum evaluation, whether in the thorax radiogram whether in CT scan is very difficult or even impossible, due to the confluence of perihilar opacity, reason why image studies can underestimate the ganglionar involvement, which is often microscopic.[53]

Pleural effusion can also be seen in 15 to 75% in PKS patients, unilateral or more often bilateral,[53-57] usually associated to the presence of Kerley B lines and the perihilar linear opacities.[53,54,56]

Regarding the aspects in magnetic resonance, some authors[58] have seen that PKS lesions (parenchymal nodules and thickening of peribronchovascular sheath) presented hypersignal in pondered sequences in T1 capturing paramagnetic contrast (gadolinium i.v.) in a significant form in most cases, what can relate with the tumor angiomatous component, containing a number of dilated capillary. Worth of note, however, that due to problems related with artefacts created

TABLE IV

Kaposi's Sarcoma Staging (ACTG)

	Progression risk	
	Small	**Big**
Tumoral mass		Edema and ulceration
	Mucocutaneous	Oral extensive
	Ganglionar	GI extensive Other organs
Immunity	CD4+ <>200 cell /µL (> 150)	CD4+ <200 cell /µL (< 150)
Systemic disease	Without previous IO	With previous IO
	Without B symptoms	With B symptoms
	E. Karnofsky > 70	E. Karnofsky < 70
		Other diseases (NHL, CNS)

TABLE V

Response criteria

Featured elements:		
	Cutaneous disease	**Pulmonary Kaposi's Sarcoma**
Current	Number of lesions	Sum of two diameters product of all lesions Number of lesions
	Lesions dimensions	
	Morphology	
Proposed	Pain	
	Edema	
	Disfigurement	
	Visceral symptoms	
	Necrosis/ulceration	
Categories: total remission. Partial remission. Stable disease. Progression.		

by respiratory and cardiac movement with the lung magnetic susceptibility, CT scan shows in better detail changes in pulmonary KS. In T2 -weighted sequences, PKS lesions presented a marked reduction of the signal intensity, what is admitted to related with alveolar hemorrhage (hemosiderin deposition) or with the tumor fibrous component.[58] This way, MR aspects suggestive of PKS lesions are: hypersignal in T1, marked reduction in the signal intensity in T2 and a strong absorption of gadolinium i.v., mainly if these lesions present a peribronchovascular distribution.[58]

In terms of differential diagnosis, before an AIDS patient showing parenchymal changes (involvement of the axial and peripheral interstitium and parenchymal nodules) associated to hilar adenopathies and pleural effusion we should raise as diagnosis hypothesis PKS, pulmonary tuberculosis and lymphoma.[53-54]

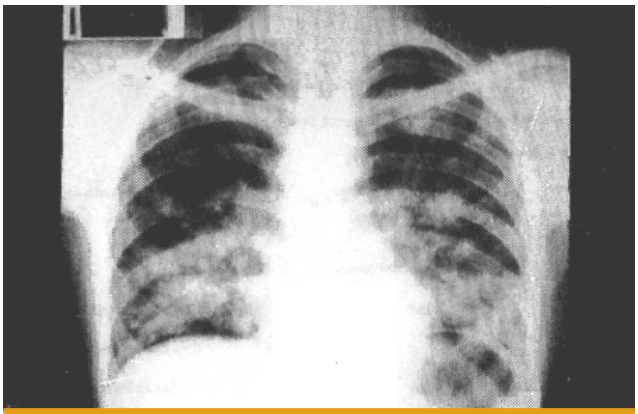
Lymphoma usually does not involve symmetrically the pulmonary parenchyma , different from PKS, and usually, the presence of bigger nodules, well defined, is more evident that the interstitial compromise.[53] The presence of adenopathies and pleural effusion makes the Pneumocystis carinii pneumonia diagnosis less likely as they are rare manifestations of this nosologic entity.[53-54] Before an isolated pleural effusion, without parenchymal changes, PKS is not the first hypothesis to consider, with the most likely etiologies being tuberculosis and lymphoma.[53]

Treatment

There are huge discrepancies in the results of different series using the same kind of therapy; such fact is due to the use of different criteria for therapeutic response. ACTG has created a scale where the response can be classified as total, partial, non-progression and progression. In this classification, are only involved objective criteria, as the number, dimension and aspects of lesions or edema (such classification is fundamentally applied to mucocutaneous KS; in the pulmonary form, the criteria are the same as for other solid tumors). However, it is discussed at present the inclusion of subjective criteria, which define the patient's quality of life and therefore, strictly related with morbidity, being an improvement of pain associated to a certain kind of lesions, an improvement of the disfigurement degree that lesions cause to the patient, and in the PKS case, an improvement of symptoms as dyspnea and cough (*Table 5*).[59]

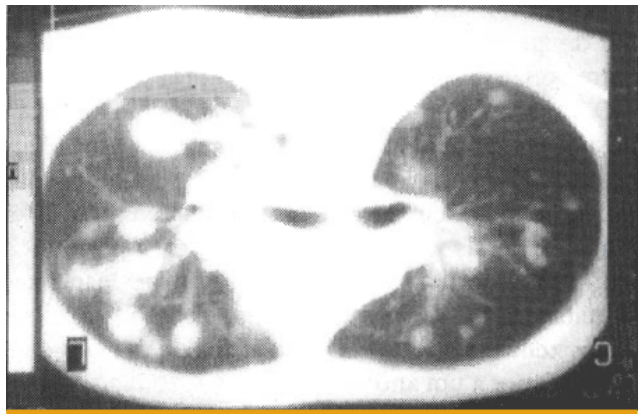
KS treatment includes the three responsible aspects for its pathophysiology: monoclonal proliferation, disruption of immunologic surveillance and deregulation of cytokines pattern. Local therapeutic or immunomodulation will not be approached.

Several compounds, potentially useful are being researched, most of them related with the control



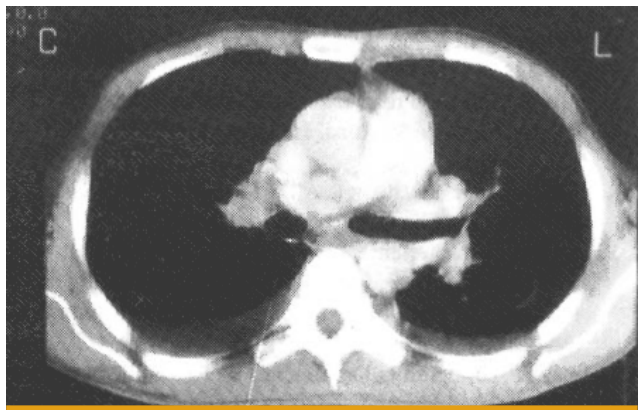
Pulmonary Kaposi's Sarcoma. Thorax radiogram: perihilar linear opacities associated to bilateral poorly defined parenchymal nodules.

FIG. 1



Pulmonary Kaposi's Sarcoma. Thoracic CT scan: thickening of peribronchovascular sheath, associated to multiple bilateral parenchymal nodules and hilar adenopathies.

FIG. 2



Pulmonary Kaposi's Sarcoma. Thoracic CT scan: subcarina adenopathies and bilateral hilar with pleural effusion of bilateral moderate volume, bulkier on the right.

FIG. 3

of cytokines deregulation, including antisense oligonucleotides (viral vectors can be used), poliTAR (would capture TAT), several interleukins (IL12), anti-angiogenic agents (TNP 470) and hormones (bHCG subunit).[60-63]

In vitro, HHV8 sensitivity to antiviral agents has revealed ciclovir great efficacy (with much lower doses than those needed for the CMV treatment), moderate sensitivity to ganciclovir and foscarnet, and acyclovir resistance.[64-66] Such data raise the hypothesis of antiviral future use in virus carriers without KS, having, however sporadic reports of regression of KS cutaneous lesions in patients with HIV infection just with therapy with foscarnet.

The current therapy, available in the clinic practice, is restricted to cytostatic polychemotherapy and the attempt of reversing immunosuppression with anti-retroviral agents (there are also sporadic reports of regression with hormonal therapy - bHCG).

KS cases of cutaneous lesions remission have been described with the introduction of triple antiretroviral combination (including a protease inhibitor).[67-69]

Chemotherapy has been the most used modality in the treatment of KS visceral forms.[70] Until a while ago, the isolated agent inducing more responses was the etoposide; such situation has changed with the introduction of liposomal anthracyclyne, with a good toxicity profile. Conventional monochemotherapy is not indicated in PKS treatment. Only liposomal anthracyclines can be tried and, if not effective, should proceed to polychemotherapy. Some studies have compared daunorubicin and liposomal doxorubicin efficacy with and so far the standard therapy, the ABV (Adriamycin + bleomycin + vincristine) coming to the conclusion, that for some that efficacy would be similar, with lower toxicity (in certain studies, liposomal doxorubicin was more effective than ABV).

Our experience refers to eight KS cases with pulmonary involvement since 1993. Four of such patients have already passed away, two patients were not treated due to the clinical situation, one has refused polychemotherapy, having been treated with vincristine and interferon without any efficacy. From the most recent five cases (since 1995) we used lipo-

somal daunorubicin in a polychemotherapy scheme (liposomal daunorubicin 40 mg/m^2 + bleomicyn 30mg in 18h perfusion and vincristine 2 mg), repeated every three weeks. One of such patients died (invasive aspergillosis).

Among the living patients, two were in C3 stage and the other two in C1, these last ones are black and one presented a generalized ganglionar disease (that in endemic form has a bad prognosis). C3 stage patients have suspended therapy at the end of six cycles, with a partial response of pulmonary and cutaneous lesions, starting then triple antiretroviral therapy, including ritonavir. The remaining two, also with partial responses, have started maintenance with liposomal daunorubicin every 2 weeks, keeping without evidence of cardiotoxicity. None of those patients has had evidence of a disease progression and in the two patients who suspended chemotherapy and started triple antiretroviral therapy, a progressive improvement of the cutaneous lesions color has been seen.

The patients clinical improvement who started therapy with protease inhibitor and have suspended chemotherapy is related with an improvement of immunity (starting $CD4^+ < 50$, at present > 100), as well as the viral load (reduction of 1.5-2 $\log_{10}$) .

In our experience, the use of an anthracycline liposomal formulation (daunorubicin) associated with bleomycin and vincristine, has enabled to get partial responses in most patients, and no severe toxicity was recorded, namely hematologic or cardiac. The disease was kept stable over a two years period in patients with a bad prognosis.

Conclusion

A brief presentation of the recent and most relevant aspects of Kaposi´s sarcoma etiology, as well as clinical and image aspects relevant in its pulmonary form was made. Lastly, the current available therapy was approached, illustrated with our short experience. ■

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