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Kaposi's Sarcoma: Malignant Tumor or Proliferative Disorder?

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Abstract—*In order to provide information on the response to treatments and clinico-pathological pattern, the clinical course of 41 patients with classic Kaposi's sarcoma (KS) was reconsidered. Twenty-six cases presented a single nodular lesion, and 15 multiple, pluricentric lesions. Surgery was the first treatment for patients with single lesions, 14 of 26 (54%) patients had recurrences: the disease-free interval ranged from a few months to 11 years. Five cases had disseminated disease, three of these were preceded by local recurrence. Cases with multiple lesions were treated by a combination of surgery, chemo- and radiation therapy (RT). In three cases spontaneous regression of disease was observed and two of these are presently disease-free. After chemotherapy and RT, many patients had complete remission of disseminated disease for up to 40 months. The drugs of first choice were vinblastine and bleomycin. Over all, only one patient died of KS, 10 years after diagnosis, nevertheless the cure rate was very poor and the final overall disease-free rate was around 30%. Proper treatment for nodular or disseminated lesions provides a fair disease-free period. Final considerations: mortality of disease is exceptional despite the 80% risk of recurrence or dissemination. Data from our series do not provide proof that adequate control of the primary single lesion could screen against recurrence: the interval between treatment of the first lesion and recurrence is sometimes exceptionally long, up to more than 10 years, and for that it is not easy to state when disease is really cured. These considerations and other analogies between KS and lymphoproliferative disorders in immunodepressed people strongly suggests the possibility of a non-malignant or even non-tumoral pattern to this disease, with implications for therapeutic strategies.*

INTRODUCTION

THE CLASSIC non-epidemic Kaposi's sarcoma (KS) is rare in Europe, but can occur sporadically, especially in Italy [1]. It is classified among malignancies, nevertheless the clinical features and chronic course are peculiar. It can disseminate but does not develop typical metastases, and mortality from this is rare. Recently some authors suggested a non-malignant, or even non-tumoral, pattern to this disease [2,3]. However, KS shows a good response to the usual tumor therapies and this high response rate gives the impression that many kinds of treatments could be effective.

This review reports only cases of classic KS, and the purpose is to verify the proper role of each treatment modality, to outline adequate therapeutic policy and finally to provide detailed information on its natural history and clinical behavior. More recently the association of KS and immune deficiency syndromes, as in AIDS or post-transplant patients, supported the possibility of a pathogenic link between virus immunodepression and cancer, thus there is an urgency to define the real category of this rare disease.

MATERIALS AND METHODS

Forty-one consecutive patients of Italian descent with KS were seen and treated at our Institute from 1966 to 1984. Clinical records of these cases were carefully reviewed and are the basis of this report. Association with immunodeficiency syndrome was excluded in this series. Cases have been divided into two major groups according to a simplified clinical classification resembling the models proposed by Mitsuyasu and Goopman [4], Taylor *et al.* [5] and Templeton and Bhana [6]: group 1, patients who

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had a single nodular lesion at initial observation and group 2, patients who had multiple lesions in one or more anatomical sites, florid lesions and/or lymph node involvement at initial observation. The term 'florid' was used when at least one of the lesions was large, infiltrative and usually not easily removable by simple wide excision.

This retrospective review deals with a great variety of clinical presentations and differences in treatment policy and therefore synoptic Tables 1 and 2 will report all cases singly. Items considered were sex, age, site of lesions, interval in months between first symptom and biopsy, type of initial treatment and adjuvant procedures. The history of any case was based on the incidence of local and distant recurrence, with an interval between initial treatment and recurrence, and information on treatment of recurrence. The final outcome evaluated the status of patients at the time of this survey, July 1986. Those patients who, in the first 10 years of follow-up, were not controlled for more than 1 year, and did not mail information questionnaires, were considered lost to follow-up. The therapeutic rationale for nodular single lesion was radical removal of the primary lesion. The surgical treatment was considered 'excision' when at least gross total removal could be achieved; on the contrary when residual macroscopic tumor was left the operation was classified as 'biopsy'. Sometimes RT was indicated postoperatively when radicality was dubious or not achieved. The main sources of RT, either adjuvant or for advanced stages, were kV X-rays, cobalt-60 and more recently MeV X-rays, the median dose-field was around 40 Gy, ranging from 28 to 62 Gy. For advanced stages, pluricentric lesions, florid lesions or lymph node involvement chemotherapy and RT, frequently in combination, were the main treatment. The drugs of first choice were vinblastine (VLB) and bleomycin (BLM), eventually associated. The typical dose was: VLB 10 mg every 2 weeks i.v. + BLM 15 mg every week i.m. Surgery was sometimes performed or attempted when multiple lesions were located in a single anatomic area, or for lymph nodes.

The response rate was evaluated in terms of survival and the disease-free actuarial interval.

RESULTS

Tables 1 and 2 report the characteristics of the whole series divided into two groups: patients with a single nodular lesion (26 cases) and patients with multiple, pluricentric lesions (15 cases). The male/female ratio was 4:1, median age 62 years (range 30–85) with no significant difference between the two groups. The foot was the initial site of diseases in 18 (70%) patients with a single lesion and was one of the involved sites in 12 (80%) patients with multiple lesions, three patients in the whole series had lesions in both feet (Nos 26, 27, 29). The median interval between first symptom and the detection of KS was different in the two groups: 5 months (range 2–24) for group 1, and 22 months (range 9–72) for group 2. The treatment of nodular KS was surgery in all cases, eight with and 18 without adjuvant RT. Besides traditional surgery, diathermic excision or laser surgery under microscope were employed in four cases (Nos 20, 21, 25, 35).

Fourteen (54%) cases had local and/or distant recurrence locally between 3 and 132 months after the first operation. Three of the eight cases treated with adjuvant RT had local recurrence; one recurrence was recorded 11 years later. The two cases (Nos 19, 24) who were given RT after intralesional operations are presently disease-free after 20 and 24 months, respectively. Finally, five cases of group 1 had disseminated pluricentric disease, three of these disseminations were preceded by local recurrence. Recurrences were treated in different ways according to extension of the disease. The initial treatment of 11 local single relapse was RT in five cases, surgery in three, chemotherapy in two and RT plus chemotherapy in one. Of these patients, six had local recurrence again while only three had disseminated spread.

Out of group 2 three cases (Nos 28, 32, 39) had multiple lesions in single areas and were treated by surgery alone; there was only one local recurrence, but all three had distant spread. The two cases (Nos 40, 41) who had laterocervical lymph node involvement had surgical excision followed by adjuvant RT: both are disease-free 36 and 50 months later, respectively. Ten cases were treated with combinations of surgery, RT and chemotherapy and all recurred or were never free of disease.

Among the whole series (groups 1 and 2) VLB alone or in combination was given to 16 patients. Six of 13 evaluable cases had complete remission (CR) lasting 6 to 65 months, three had partial response and four no response. Other drugs which revealed possible efficacy were vindesine, used in one case (No. 25) with CR for 20 months, and perhaps VP-16 (Nos 30, 36, 37), always used after conventional chemotherapies, resulting in stable disease for a short time only.

Two cases (Nos 35, 38) both in the 50s had cerebral ischemia; the former had irreversible hemiplegia, the second died: autopsy did not reveal cerebral or visceral KS involvement.

In three cases spontaneous regression was observed: two cases (Nos 29, 32) had regression of untreated recurrences, and one (No. 36) had regression before treatment; in fact the patient had multiple nodules in the foot and poplitis of the left limb which disappeared without any treatment, but after 2 years similar lesions reappeared fast growing

Table 1. *Kaposi's sarcoma. Characteristics of the series (I). Group* 1: *patients with a single nodular lesion*

No.	Sex	Age	Site	Interval*	Main treatment and adjuvant	Local recurrence and treatment†	Distant recurrence sites and treatment†	Status‡	
1	M	68	Foot	(24)	Exc.skin graft			NED	(61)
2	M	46	Foot	(3)	Exc.skin graft			NED	(74)
3	M	74	Foot	(12)	Exc.skin graft			†NED	(33)
4	M	74	Foot	(10)	Exc.			†NED	(90)
5	M	48	Tongue	(3)	Exc.	(92)RT		NED	(108)
6	M	60	Hand	(4)	Exc.			NED	(136)
7	F	37	Foot	(2)	Exc.			NED	(144)
8	M	30	Ear	(?)	Exc.	(3)(17)Exc.	(18)Foot—VLB+BLM to CR	NED	(84)
9	M	47	Foot	(?)	Exc.ADR+VCR	(48)RT+VLB to PR		LWD	(140)
10	M	67	Foot	(2)	Exc.VLB		(56)Elbow+nodes —Exc.s	NED	(69)
11	M	79	Arm	(?)	Exc.RT		(31)(40)Foot and gluteus—Exc.s	NED	(43)
12	M	59	Ear	(?)	Exc.	(5)Exc.	(5)Arm—Exc.+RT	NED	(52)
13	M	57	Hand	(?)	Exc.RT	(132)(180)RT		NED	(197)
14	M	62	Foot	(?)	Exc.	(13)RT(27) VLB+VCR		LOST	(28)
15	M	75	Foot	(2)	Exc.	(1)RT(20)Exc.		LOST	(20)
16	M	49	Foot	(24)	Exc.			LOST	(1)
17	M	48	Foot	(?)	Exc.RT			NED	(14)
18	F	57	Leg	(?)	Exc.RT			NED	(19)
19	M	49	Foot	(?)	Biop.RT			NED	(24)
20	M	85	Foot	(2)	Exc.(diathermic)			+NED	(117)
21	M	69	Foot	(?)	Exc.(diathermic)	(72)VLB up to CR		NED	(120)
22	F	81	Foot	(?)	Exc.RT	(16)Laser exc.		NED	(20)
23	F	75	Ankle	(?)	Exc.	(60)(72)RT twice		NED	(88)
24	M	83	Foot	(6)	Biop.RT			NED	(20)
25	F	67	Foot	(12)	Exc.RT	(9)Vindesine(38)RT		LOST	(38)
26	M	59	Foot	(12)	Exc.	(62)Exc.	(85)Feet—VLB+BLM/ ADR+DTIC	+DOD	(112)

In parentheses, intervals in months: *from the first symptom to biopsy, †from biopsy to recurrence, ‡from biopsy to last control. Abbreviations in alphabetical order: ADR = adriamycin, Biop. = biopsy, BLM = bleomycin, CR = complete remission. +DOD = dead of disease, DTIC = imidazolcarboxamide, Exc. = excision, LOST = lost to follow up, LWD = alive with disease, NED = no evidence of disease, +NED = dead with no evidence of disease, PR = partial remission, RT = radiation therapy, VCR = vincristine, VLB = vinblastine.

in the entire limb, and at that time the biopsy confirmed the diagnosis of KS.

In Fig. 1 are reported the curves of survival of the patients regardless the cause of death. Only one patient died of KS (No. 26) 10 years after the diagnosis, for neoplastic cachexia due to progression of disseminated florid lesions, and for this reason the curves of expected survival and survival of KS are almost superimposable. The 12-year actuarial free of recurrence interval, divided into the two groups, is reported in Fig. 2, where the interval between diagnosis of KS and onset of local or systemic recurrence is considered.

DISCUSSION

The natural history of classic KS is well known and data of our series confirms the unusual pattern of this disease. Examining the end results of the 41 cases presented in this paper two major considerations emerge: that the typical cancer therapies like surgery, chemotherapy and radiation therapy have little impact on the cure rate, and that there exists a clear discrepancy between rare mortality and poor curability. Patients with single lesion (group 1), revealed a better disease-free interval compared with patients with disseminated disease (group 2), but the latency of symptomatic disease prior to biopsy is of a few months for single lesions and about 2 years for multiple lesions. Results of treatments emphasize the role of adequate surgery, eventually followed by RT for resectable lesions, even if located at distant sites or with minimal lymph node involvement: cases 10, 11, 40, 41 were controlled locally, distantly and in the lymph nodes by surgery plus RT only. It is well known that RT [7, 8] and chemotherapy [9–12] are effective, and our experience seems to confirm this point, but local or disseminated recurrences can occur even after a long interval, and spontaneous regression is also possible, therefore it is difficult to state when the disease is really cured, and to evaluate the real effect of therapies. Treatments are effective in improving

Table 2. Characteristics of the series (II). Group 2: patients with multiple, disseminated or lymph node disease

No.	Sex	Age	Site of the lesions	Interval*	First treatment	Recurrence, site and treatment†	Status‡	
27	F	68	Feet and legs (florid)	(30)	Biop+RT	(11)Foot—RT	LOST	(14)
28	F	52	Foot and heels	(12)	Exc.s	(9)(60)Exc.s(74)feet and leg—VLB to CR	NED	(90)
29	M	65	Foot	(?)	Biop—RT	(7)Feet—RT+VLB(30)(65) spontaneous regress.	NED	(101)
30	M	72	Foot and leg	(?)	Biop.—VLB	(5)RT(11)Ear—RT(23)nodes —VLB—VP16	LWD	(43)
31	M	65	Inferior limb (florid)	(20)	Biop.—RT+VLB+BLM	(25)CPM+VCR+ADR(32) amputation(84)nodes	LWD	(111)
32	F	63	Heel	(?)	Exc.s	(3)Contralateral limb— spontaneous regress.	NED	(18)
33	M	51	Inferior limbs	(9)	Biop.—VLB+BLM	(46)RT(54)RT never NED ((60)lichen planus)	LWD	(73)
34	M	57	Hand and inf.limb (florid)	(36)	Biop.+VLB	(10)RT never NED	LWD	(44)
35	M	57	Foot,hand,arm	(?)	Laser biop.—VLB	(4)RT—never NED	LWD	(56)
36	M	54	Inferior limb (florid)	(24)	Biop.—VLB—RT—BLM +DTIC—VP16— never NED		LWD	(108)
37	M	62	Sup. and inf.limbs	(72)	Melphalan+DTIC in perfusion§—VLB +BLM to CR	(24)VLB—VP16+RT	LWD	(43)
38	M	52	Sup. and inf.limbs	(?)	VLB+DTIC never NED		+WD	(10)
39	M	53	Ear (florid)	(?)	Exc.s	(11)Limbs and nodes—BLM —VCR—CPM, never NED	LWD	(145)
40	M	76	Eyelid and cervical nodes	(12)	Exc.+RT		NED	(36)
41	M	70	Cervical nodes	(?)	Exc.+RT		NED	(49)

In parentheses, intervals in months: *from the first symptom to biopsy, †from biopsy to recurrence, ‡from biopsy to last control. §Hyperthermic perfusion in extracorporeal circulation of the superior limb.

Abbreviations in alphabetical order: ADR = adriamycin, Biop. = biopsy, BLM = bleomycin, CR = complete remission, CPM = cyclophosphamide, DTIC = imidazolcarboxamide, Exc. = excision, LOST = lost to follow up, LWD = alive with disease, NED = no evidence of disease, Node = lymph node, RT = radiation therapy, VCR = vincristine, VLB = vinblastine, +WD = dead with disease, but not for disease.

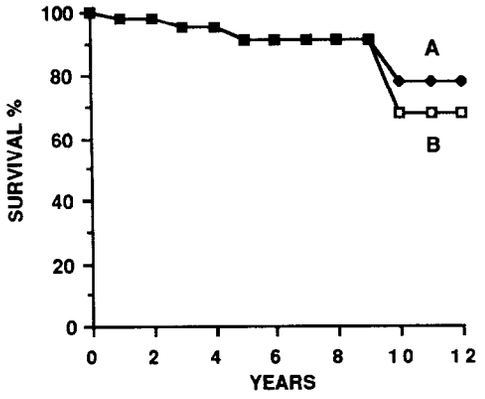

Fig. 1. Twelve-year actuarial survival. A: Survival of patients who did not die of KS. B: Survival of patients regardless the cause of death.

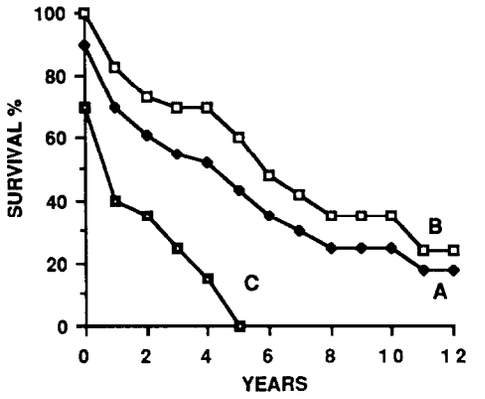

Fig. 2. Twelve-year actuarial free of disease interval. A: overall. B: Patients with single lesion. C: Patients with multiple lesions.

the performance status of the patients but have little influence on survival which is almost equal to the normal population in the same cohort of sex, age and socio-geographical area.

Since its identification, from a pathologic point of view, KS was classified among the malignancies of mesenchymal descent [13–15] but the clinical course and response to therapies are so unusual that from a clinical point of view it is hard to assimilate classic KS to soft tissue sarcomas, and this disease is regularly excluded in the treatment protocols for soft tissue sarcomas. The clinical history merits a pathological reassessment: this request is not a mere problem of classification, because the actual inclusion of Kaposi's among sarcomas has some implications on therapeutic rationale and mechanism on oncogenesis. Starzl and Makowka of the group in Pittsburgh [16, 17] defined a recent pathologic entity of post-transplant lymphoproliferative disorders (PTLD) with an appendix on Kaposi's sarcoma. Moreover, the same group of diseases is sometimes associated with acquired immunodeficiency syndromes. The association of viruses and KS was already well known even in the years preceding the detection of AIDS [18], and recently the Pittsburgh group [17] confirmed a reactivation of cytomegalovirus (CMV) concomitant infections in post-transplant patients with KS. In favor of this viral pathogenesis is that KS showed some grade of response to interferon therapy [19, 20]. These considerations support the existence of virus-associated lymphoproliferative disorders [21], frequent in patients who suffer from immunodepression, and KS more likely belongs to this group.

Comparing the final conclusions drawn by our series with the data of KS in immunodepressed populations a few significant points emerge:

1. Soft tissue sarcomas, as almost all malignant tumors, do not show any drastic behavior changes in immunodepression, whereas KS, which is a slow growing non-lethal disease in its classic pattern, is quite different, fast, aggressive and lethal when epidemic [22].
2. Immunosuppression can enhance the occurrence of lymphoproliferative disorders up to tens of times that in the normal population, and KS is reported to occur up to 500 times more frequently in the same goup of immunodepressed patients than the control population [23]. These diseases, under the name of lymphoma and sarcoma, respectively, constitute most of the clinical material which supports the oncogenic potential of virus and immunodepression.
3. Spontaneous but not stable regression is possible in classic KS, and Starzl *et al.* [16] also documented complete and stable regression of multifocal KS in organ transplant recipients, by drastic reduction of immunosuppressive therapy, and also some lymphoproliferative disorders had the same behavior in an immunosuppressed population.

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