HIV-related Kaposi's Sarcoma with Musculoskeletal Involvement in the Modern Antiretroviral Era

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Abstract. *Aim: To describe the patterns of disease and clinical outcomes of MSK-KS in people living with HIV in the era of (combination anti-retroviral therapy cART). Patients and Methods: We reviewed our prospectively collected dataset of patients with HIV with biopsy-proven KS; 17 out of 1,489 seropositive patients were identified with subsequent evidence of MSK involvement by KS. We collected data with regards to clinicopathological parameters and radiological patterns of disease. Results: Fourteen patients (82.4%) had AIDS Clinical Trials Group T1 stage disease at presentation including four (23.5%) with non-nodal visceral disease. At the time of MSK-KS diagnosis, more than 80% of 14 patients had excellent HIV control. The median interval between initial KS to MSK-KS diagnosis was 3.3 years. Five-year overall survival rate from initial KS diagnosis was 76%, and 60% from MSK-KS diagnosis. The majority of patients were asymptomatic and MSK-KS involvement was demonstrated during imaging prompted by progression of their mucocutaneous KS. The majority of lesions were lytic with cortical involvement on cross-sectional imaging, whereas a soft-tissue component was commonly associated with long-bone involvement. Conclusion: MSK-KS continues to be a rare entity in the modern era of cART, however patients appear to experience significantly improved survival.*

Kaposi's sarcoma (KS) is a malignant neoplasm of probable lymphatic endothelial origin which is strongly associated pathophysiologically with human herpes virus-8. In people living with human immunodeficiency virus (PLWH), KS predominantly manifests with mucocutaneous lesions, but can often involve other organs such as lymph nodes, as well as the respiratory and gastrointestinal systems. In an autopsy series from the 1980s, the most common sites of visceral involvement by acquired immunodeficiency syndrome (AIDS)-related KS were lymph nodes (72% of cases), lung (51%), gastrointestinal tract (48%), liver (34%), and spleen (27%) (1). Another autopsy series also from the era prior to combination antiretroviral therapy (cART), showed that at the time of death, only 25% of patients with AIDS-KS had KS confined to the skin and conversely 29% had visceral involvement without any skin lesions (2). Musculoskeletal (MSK) involvement by KS has been recognised as a rare form of disease associated with a very poor prognosis in patients with poorly controlled HIV (3). We report the largest series of MSK-KS in PLWH in the cART era, focusing on clinical outcomes and radiological patterns of involvement.

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Patients and Methods

At the National Centre for HIV malignancies at the Chelsea and Westminster Hospital, we prospectively collect routine data on all individuals who attend. This prospective dataset includes 1484 PLWH diagnosed with KS since 1986, of whom 643 were diagnosed with KS after 1996 when cART became routinely available in the UK. From this dataset, 17 patients who developed MSK involvement were identified and their clinicopathological and radiological features were collated.

Overall survival was calculated from the day of KS diagnosis or MSK-KS diagnosis until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier (4). The log-rank method was used to test for the significance of differences in survival distributions (5).

Results

Seventeen HIV seropositive patients were identified with biopsy-proven Kaposi's sarcoma and subsequent evidence of musculo-skeletal (MSK) involvement by KS. At initial KS diagnosis, the median age was 34 years (range=21-52 years); the clinicopathological features are shown in Table I.

Fourteen (82%) were male, 10 (59%) of black African descent, 6 (35%) Caucasian and one (6%) of Indian origin. The median values for cluster of differentiation 4 ($CD4^+$) lymphocyte count was 186/mL (range: 10-710) and all but

Table I. *Clinical information of patients at initial diagnosis of Kaposi's sarcoma (KS Dx); all biopsies were cutaneous, except for cases 5 and 16, that were lymph node biopsies.*

Gender	Age (years)	Ethnicity	Biopsy (grade)	ACTG Stage at KS Dx	Initial sites	CD4+ at KS Dx (/mm^3)	Plasma HIV VL (copies/ml)	Plasma HHV8 (copies/ml)	Survival (months)
1, M	22	Caucasian	Angiomatoid	T1 I0 S0	Skin, palate, oedema	186	52	0	15
2, M	21	Caucasian	Plaque	T1 I1 S1	Skin, LN, palate	72	119935	?	4.5
3*, M	40	Caucasian	Plaque	T1 I0 S0	Skin, LN, palate	90	?	?	86
4*, M	42	Black African	Nodular	T1 I1 S1	Skin, lung, liver, gastric, edema	?	?	?	157
5, M	52	Black African	Nodular	T1 I0 S1	LN, lung	196	1128	170	65
6, M	34	Black African	Nodular	T1 I0 S0	Skin, oedema	287	?	0	113
7, M	42	Indian	Patch	T0 I1 S1	Skin	110	149000	?	90
8, F	42	Black African	Plaque	T1 I0 S0	Skin, oedema	480	24000	0	42
9, M	31	Caucasian	Patch	T1 I1 S0	Skin, LN, lung	50	121000	0	18
10*, M	26	Caucasian	Nodular	T0 I0 S1	Skin, LN	330	500000	19000	74
11*, F	33	Black African	Plaque	T1 I1 S0	Skin, palate, lung	10	400000	110000	103
12*, M	37	Black African	Angiosarcomatoid	T1 IX S1	Skin	?	?	?	153
13*, F	25	Black African	KS, unclassified	T1 I0 S1	Skin, palate, LN, oedema	156	95811	29000	22
14*, M	37	Black African	KS, unclassified	T1 I1 S0	Skin, oedema	?	?	?	189
15*, M	31	Caucasian	KS, unclassified	T1 I0 S0	Skin, LN	416	39000	?	49.5
16*, M	29	Black African	KS, unclassified	T0 I0 S0	Skin	710	<40	9300	94
17*, M	35	Black African	KS, unclassified	T1 I1 S0	Skin, oedema	?	?	?	151

ACTG: AIDS Clinical Trials Group; M: male; F: female; VL: viral load; LN: lymph node; CD4+: cluster of differentiation 4 lymphocyte count; HHV8: human herpes virus 8 load; Survival: overall survival from initial KS Dx; ?: Unrecorded information. *Alive/censored patient.

one had detectable HIV viraemia with a median plasma HIV viral load of 95811 copies/mL. All 17 patients had cutaneous KS at diagnosis and in addition, seven (41%) had nodal disease, four (23%) palatal KS, four (23%) pulmonary KS and one (6%) gastric and liver KS. Fourteen patients (82%) had AIDS Clinical Trials Group T1 stage disease at presentation, including four (23%) with non-nodal visceral disease. None had MSK involvement at first presentation of KS. Initial treatment for KS was cART, and systemic chemotherapy was also administered at presentation of KS for those with T1 stage disease (6).

At the time of diagnosis of MSK involvement by KS, the median age of patients was 42 years, and the median interval between initial KS presentation to MSK-KS diagnosis was 3.3 years (maximum 9.2 years). At MSK-KS diagnosis, all patients were prescribed cART and only two had detectable plasma HIV viraemia. The median CD4+ cell count was 240/ml. The clinicopathological features at the time of MSK involvement by KS are shown in Table II.

Four patients presented with symptomatic MSK involvement, three with metastatic spinal cord compression, and one patient developed metatarsal pain. The diagnosis of MSK-KS was made in the remaining 13 (76%) following radiological restaging investigations for progressive cutaneous KS with cross-sectional imaging modalities [computed tomography (CT) and magnetic resonance imaging (MRI)]. The diagnosis of MSK-KS was confirmed by biopsy in six patients where the differential diagnosis was considered uncertain (four bone and soft tissue biopsies and two bone marrow aspirate and trephines).

The appendicular skeleton was involved in 12 (71%) patients. The pelvic bones (Figure 1) were most frequently affected (35%), whereas femoral involvement was noted in four (23%) patients. Axial skeletal involvement was noted in nine (53%) patients. Vertebral deposits were always present when the axial skeleton was involved (Figure 2). In four (23%) patients, both axial and appendicular involvement was detected. In 13 patients (75%), MSK-KS presented as either solitary or multiple lytic osseous lesions ranging from 2 mm to 3 cm in size. The majority of lytic osseous lesions had cortical involvement (cortical thinning or erosions). Complete cortical destruction was evident in three (18%) patients. No sclerotic lesions were identified in our cohort. An aggressive periosteal reaction (Codman's or sunburst type) was present in two (12%) patients. In four patients (23%), a soft-tissue component, most commonly associated with long-bone involvement (femur and tibia), was evident on imaging.

Despite cART, systemic chemotherapy and radiotherapy, seven (41%) patients died of progressive KS. The 5-year overall survival rate from initial KS diagnosis was 76% [95% confidence interval (CI)=48-90%], and 60% (95% CI=31-80%) from MSK-KS diagnosis (Figures 3 and 4). The presence of non-nodal visceral metastases was not a prognostic factor for overall survival from KS diagnosis

Table II. *Clinical information of patients at musculoskeletal (MSK) involvement by Kaposi sarcoma (KS) at diagnosis (Dx).*

Gender	Age at MSK KS Dx, years	CD4+ at MSK-KS Dx (/mm^3)	Plasma HIV VL (copies/ml)	Plasma HHV8 (copies/ml)	Time from KS Dx (months)	Biopsy-proven MSK-KS	Survival (months)
1, M	24	441	<50	630000	15	No	0
2, M	21	121	<50	?	0.5	No	4
3*, M	42	263	<40	330000	25	No	61
4*, M	49	165	<40	0	92	No	65
5, M	56	232	<40	0	40	No	24
6, M	42	240	<40	0	110.2	Yes	3
7, M	46	68	13204	4100	46.5	Yes	44
8, F	45	47	<50	0	40.7	No	1
9, M	32	23	185468	28700	12	No	6
10*, M	27	504	<50	2200	1.8	No	73
11*, F	34	52	<50	0	13	No	90
12*, M	43	566	<50	200	80	Yes	73
13*, F	26	331	<40	6985	9	No	13
14*, M	43	?	?	?	72	Yes	117
15*, M	31	690	<40	590	4	No	44
16*, M	33	519	<40	2762	45.5	Yes	48.5
17*, M	45	?	<40	?	140	Yes	11

M: Male; F: female. CD4+: CD4+ lymphocyte count; VL: HIV viral load; HHV8: human herpes virus 8 load; Survival: overall survival from MSK-KS Dx. ?: Unrecorded information; *Alive/censored patient.

[relative risk (RR)=1.24, 95% CI=0.24-6.42, p=0.8] nor from MSK-KS diagnosis (RR=1.34, 95% CI=0.24-7.35, p=0.74). Similarly, time from KS to MSK-KS diagnosis was not a prognostic factor for overall survival from KS diagnosis (RR=0.9782, 95% CI=0.95-1.0058, p=0.12), nor from MSK-KS diagnosis (RR=0.99, 95% CI=0.97-1.02, p=0.89).

Discussion

KS at unusual sites including MSK-KS has been described but is rare. At the National Centre for HIV-associated malignancy, we have cared for 1,484 HIV seropositive patients with KS since 1986, including 643 initially diagnosed with KS in the cART era, and identified 17 patients (1.1%) from our prospective dataset who had radiological evidence of MSK involvement by KS. In our series, no patients had MSK involvement at initial KS presentation. The median interval from KS diagnosis to MSK-KS diagnosis was 3.3 years and at the time of MSK involvement, the median CD4+ cell count was 240/mL and 82% had fully suppressed plasma HIV viral load. These immunological parameters suggest that the development of MSK involvement reflects some degree of immune autonomy of KS.

A comprehensive literature review of MSK involvement by KS was published in 2006 by Caponetti *et al*. (3), with a total of 66 patients, including 28 with AIDS-related KS. The majority of the AIDS patients with KS were diagnosed in the pre-cART era and only five were receiving cART at the time of MSK diagnosis, often with poor compliance and CD4+ cell counts of less than 100/ml. The authors concluded that the survival following diagnosis of MSK involvement by AIDS-KS was very short, with death occurring within days or weeks. In contrast, the 5-year overall survival rate in our patients following diagnosis of MSK-KS was 60%. Whilst it is tempting to suggest that the improvement in survival is attributable to treatment with a combination of cART and chemotherapy, most patients already had fully suppressed HIV viraemia and normal CD4+ counts at the time of MSK-KS diagnosis.

Furthermore, in the review by Caponetti *et al*. the majority of patients with AIDS-KS presented with symptoms, predominantly pain, and a significant proportion presented with MSK-KS at the same time as initial cutaneous/mucosal KS. In our study, all patients had a prior diagnosis of cutaneous KS and only four presented with symptomatic MSK disease. Whether the detection of asymptomatic MSK-KS lesions in our study represents a true effect of exposure to cART or is attributable to more frequent cross-sectional imaging within the context of centralised follow-up remains uncertain.

The radiological features of MSK-KS are lytic osseous lesions or soft-tissue masses causing osseous erosion or destruction. Osteolysis is the predominant feature on conventional radiography and CT. It manifests as uniform rarefaction, cortical lytic lesions or complete osseous destruction (3, 7). Lytic lesions were also the predominant

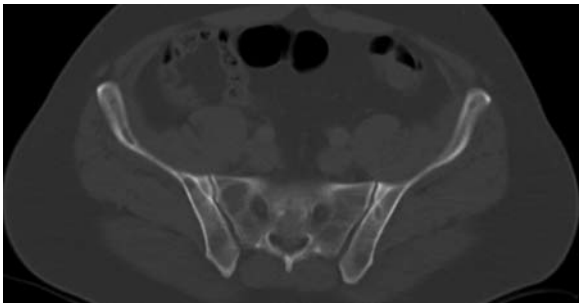

Figure 1. *Multiple well-defined lucent bone lesions involving the pelvic bones on computed tomography (patient no. 15).*

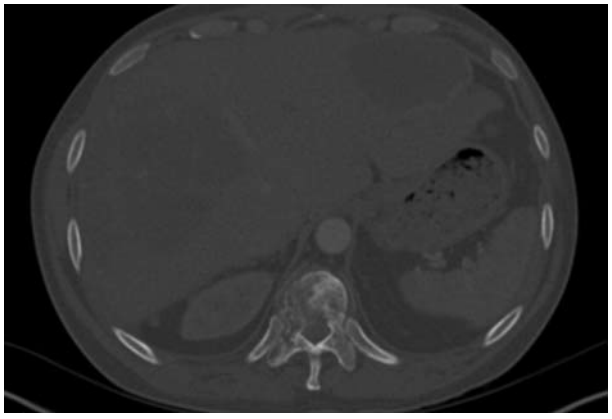

Figure 2. *Destruction of the T10 vertebral body by Kaposi sarcoma and liver metastases on computed tomography (patient no. 4).*

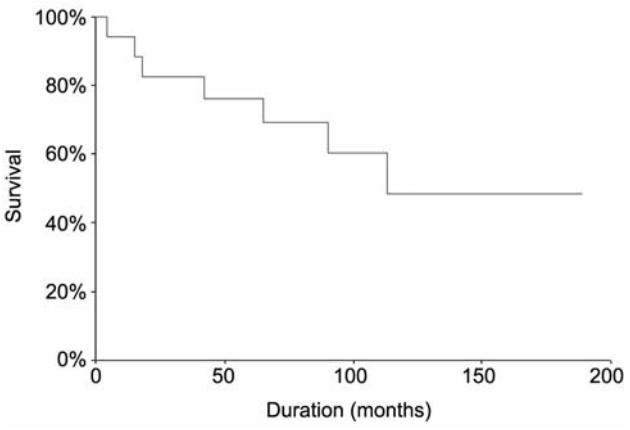

Figure 3. *Overall survival from Kaposi sarcoma at diagnosis. 5-Year overall survival=76% (95% confidence interval=48-90%).*

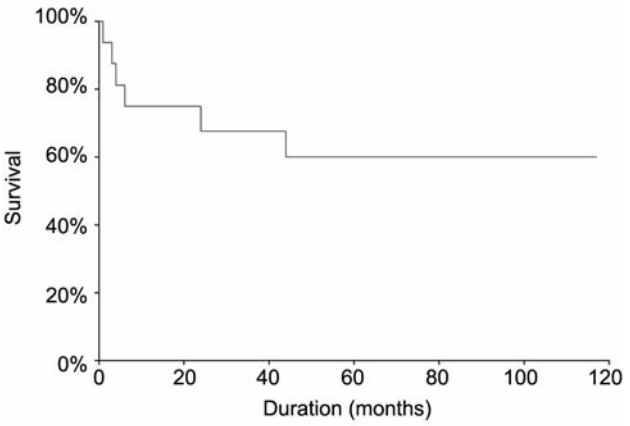

Figure 4. *Overall survival from musculoskeletal involvement by Kaposi sarcoma at diagnosis. 5-Year overall survival=60% (95% confidence interval=31-80%).*

features of MSK involvement by KS in our series. Sclerotic lesions have been described, albeit rarely (8); none were identified in our cohort. CT provides detailed characterization of lytic bone changes and has the advantage of accurately identifying osteolytic and soft-tissue lesions for targeted biopsy (9, 10). MRI is exceptional at depicting bone marrow abnormalities, for evaluation of intra-osseous tumour extension and assessing extrinsic soft-tissue masses. MRI signal abnormalities are dependent on the extent of mineralization. Non-mineralized (lytic) lesions typically have intermediate T1 and high T2 signal. Mineralized lesions have low T1 and T2 signal. The associated peri-lesional oedema is intermediate on T1 and high on T2/short T1 inversion recovery signal. MRI marrow signal abnormalities can, however, be difficult to differentiate from those of lymphoma and infection (9, 10). Scintigraphy can be useful in differentiating MSK-KS from infection and lymphoma. Musculoskeletal KS has been reported to demonstrate uptake with thallium-201 but not with gallium-67. Infection and lymphoma are typically gallium-avid (9, 11). Finally, little is known about ^{18}F-fluorodeoxyglucose positron emission tomography (PET) appearance of KS; however, in a small retrospective study, PET imaging was associated with a 92% true-positive rate in patients with KS when correlated with a confirmed KS pathological diagnosis, indicating a potentially emerging role for PET in the diagnostic work up of patients with KS that warrants further studying (12).

The radiological differential diagnosis of MSK-KS includes bacillary angiomatosis, tuberculosis, osteomyelitis, cryptococcosis, pyogenic granuloma, hemangioendothelioma, angiosarcoma, arteriovenous malformation and lymphoma (3, 7, 13, 14). Complementary use of conventional radiography (X-rays), multi-detector computed tomography, MRI and scintigraphy assists differentiation. However, in view of the

wide differential diagnosis and the different clinical management, a biopsy should be the gold-standard confirmatory test, as imaging alone is not adequate for reliably distinguishing the above clinical entities in diagnostically challenging cases.

Conclusion

MSK involvement by KS in PLWH is rare and appears to be associated with a better prognosis than previously described for patients treated chiefly in the pre-cART era. This improvement in outcome may be accounted for by better treatment of both HIV and KS, but may also relate to case ascertainment as most patients in our cohort were diagnosed when asymptomatic. Nevertheless, the 5 year overall survival of 76% from initial KS diagnosis and 60% from MSK diagnosis compare unfavorably to published data. Of note, the 5-year overall survival from initial KS diagnosis using a stage-stratified treatment approach in our cohort was 92% for T0 stage KS and 83% for T1 stage KS (6), indicating substantially improved outcomes in patients with KS in the cART era.

Conflicts of Interest

The Authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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