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ORIGINAL ARTICLE

Classic Kaposi's sarcoma: A review of 156 cases

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ABSTRACT

Background: Kaposi's sarcoma (KS) is a reactive, multifocal, multicentric, angiogenic neoplastic proliferation that is thought to originate from endothelial cells that are infected with human herpesvirus-8 (HHV-8). This report examines a cohort of patients with classic Kaposi's sarcoma (KS) evaluated at the national institute of oncology over the 13-year period.
Methods: A retrospective analysis of 156 patients with classic KS, between January 2000 and November 2013, was performed. This study focused on the clinical presentation, staging, diagnosis, and treatment of classic KS.
Results: One hundred fifty-six patients (median age 69 and 115 male) were enrolled into the study. Median age at diagnosis was 69 (range: 32–95 years). Male/female ratio was 2.80. The most common location was the lower limbs. There were 75 stage I patients (48.1%), 8 stage II patients (22.4%), 31 stage III patients (19.9%) and 15 stage IV patients (9.6%). Surgery was the most common local treatment method (43%). 44 patients (28.2%) received radiotherapy (RT) at diagnosis. Cytotoxic treatment with chemotherapy or interferon-α was administered in 57 patients. Visceral involvement was observed in 10 patients (lung: nine patients, liver: one patient) and bone metastasis occurred in two patients at relapse.
Conclusion: This study is one of the largest reported series. Further studies are required and it will be important to standardize the assessment of disease activity and clinical response.

Introduction

Kaposi sarcoma (KS) is a vascular endothelial malignancy and the neoplastic cells are closely related to lymphatic endothelial cells.[1] It occurs predominantly on the skin, but can involve virtually any organ, perhaps except the brain. KS was quite rare in most of the Western world prior to AIDS. The initially described form, now known as classic KS, predominantly involves lower extremities of elderly men, and is found mostly in Ashkenazi Jews or in individuals living near the Mediterranean Sea. A more aggressive form of KS, now called endemic KS, was subsequently recognized in Africa. This form can occur earlier in life, often in the third or fourth decades, frequently involves the lymph nodes, and occurs in a higher percentage of females than classic KS. The term “epidemic KS” is used to describe KS arising in HIV-infected patients. It is generally more clinically aggressive than classic KS. KS can also occur in transplant recipients. Human herpesvirus (HHV-8) is the etiologic agent for all forms of KS.

The purpose of this study was to evaluate demographics, tumor characteristics, and treatment modalities of patients with classic KS who have been followed up at different centers.

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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Materials and methods

A retrospective analysis of patients referred to the tertiary hospital between January 2000 and November 2013 with a diagnosis of classic KS was performed. In this study, 176 Turkish patients with KS were evaluated. Classic KS was proven by cutaneous biopsies and immunohistochemical staining. Serum samples from all patients have been tested for antibodies to HIV, using ELISA and Western Blot. HIV seropositive individuals have been excluded, as well as patients who had received immunosuppressive therapy prior to KS development. The study population consisted of cases of histologically proven 156 classic KS excluding posttransplantation (*n*: 2 patients), immunosuppressive therapy (*n*: 14 patients) and epidemic KS (*n*: 10 patients). Data were collected from the patient's medical files and the following parameters were recorded: gender, origin, age at diagnosis, anatomic distribution (size, location), immune compromised conditions, clinical course, progression date and date of deaths or last follow-up if date of death unknown and treatment modalities. Based on lesion distribution and disease progression a classification system for staging classic KS has been proposed.[2] It describes four stages (I–IV) based on skin lesions, their localization, the presence or absence of complications and visceral involvement.

- Stage I (maculonodular stage) – Small macules and nodules primarily confined to the lower extremities
- Stage II (infiltrative stage) – Plaques mainly involving lower extremities, sometimes associated with a few nodules
- Stage III (florid stage) – Multiple angiomatous plaques and nodules involving the lower extremities that are often ulcerated
- Stage IV (disseminated stage) – Multiple angiomatous nodules and plaques extending beyond the lower extremities

Data evaluated

Data were recorded on patient age, gender; a clinical appearance of classic KS; clinical stage; how long KS had been diagnosed; tumor localization; histopathological traits and treatment methods.

Results

Patients characteristics

One hundred fifty-six patients were identified to have a diagnosis of classic KS between January 2000 and November 2013. Approximately 26.3% of the patients were females and 73.7% of them were males. Male-to-female ratio was 2.80 (115/41). Median age at diagnosis was 69 (range: 32–95 years). All patients were Turkish origin but no ethnic characteristics, especially Jewish, were identified. No familial cases of Kaposi sarcoma were found. Patient characteristics are summarized in Table 1.

Clinical features and location of lesions

Excisional biopsy was the most common diagnostic procedure. The clinical pattern of classic KS in our patients was characterized by its extreme variability and represented all stages of KS: 73 patients (46.8%) in maculonodular stage, 34 patients (21.8%) in infiltrative stage, 31 patients (19.9%) in florid stage and 13 patients (8.3%) in disseminated stage. Tumor localization is summarized in Figs. 1 and 2.

Table 1 Patients characteristics.

Characteristics	
Age at diagnosis	
Median	69
Range	32–95
Age distribution	*n* (%)
30–40	6 (4)
41–50	10 (7)
51–60	22 (14)
61–70	52 (33)
71–80	49 (31)
81–95	17 (11)
Gender	
Male	115 (73.7)
Female	41 (26.3)
Tumor localization	
Lower extremity	92 (59)
Upper extremity	22 (14.1)
Both upper and lower extremities	26 (16.7)
Trunk	1 (0.6)
Head and necks	5 (3.2)
Genitalia	3 (1.9)
Disseminated body	7 (4.5)
Stage	
I	75 (48.1)
II	35 (22.4)
III	31 (19.9)
IV	15 (9.6)
HHV-8	
Positive	24 (15.4)
Negative	11 (7.1)
Unknown	121 (77.6)

Clinical course and treatment

The median follow-up was 21.5 months (range 2–319 months). The median DFS was 35 months (95% CI: 30–39). Surgery was the most common local treatment method (43%). 44 patients (28.2%) received radiotherapy (RT) at diagnosis. With a predominance of surgery and RT combination, 33 patients (21.8%) had a multidisciplinary approach. Median RT dose was 800-Gy (range 600–4000 Gy). Interferon-α was the most common immunomodulator regimen. Cytotoxic treatment with chemotherapy or IFN is summarized in Fig. 3. Observation without specific treatment was seventeen point three percent (17.3%). Relapse rate was 34%. Visceral involvement was observed 10 patients (lung: nine patients, liver: one patient) and bone metastasis occurred in two patients at relapse.

Discussion

The current study represents a large retrospective review of 156 patients with a diagnosis of classic KS seen in our country over the 13-year period (2000–2013). Classic KS is relatively rare and only small numbers of patients are treated at each center. Our study is one of the largest series in the literature. Classic KS characteristically appears as pigmented macular–papular lesions on mucocutaneous surface. It is typically dark blue or purple. Lesions may present as solitary nodules or plaques and tumors to a size of several centimeters (Fig. 2). Lesions occurred in our study on the distal extremities, particularly the lower legs and feet. In general, gastrointestinal (GI) tract/oral mucosal involvement is less common than with acquired immunodeficiency syndrome (AIDS)-related KS.[3–5] Classic KS typically first presents in men (and women, although less often) in their 60s and 70s but has been described in patients in their teens and 20s, as well.[6,7] Only 4 to 8 percent of cases develop in individuals younger than age 50.[8–10]

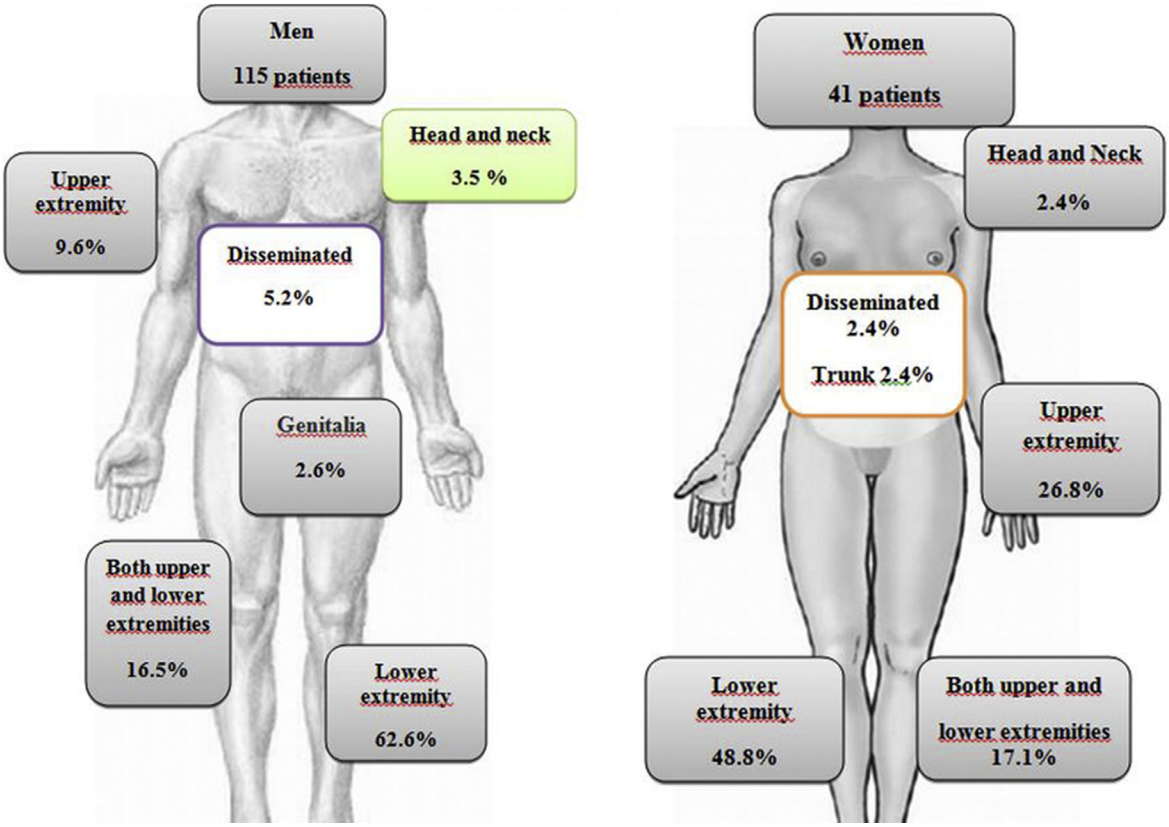

Fig. 1 Distribution of localization of classic KS by sex.

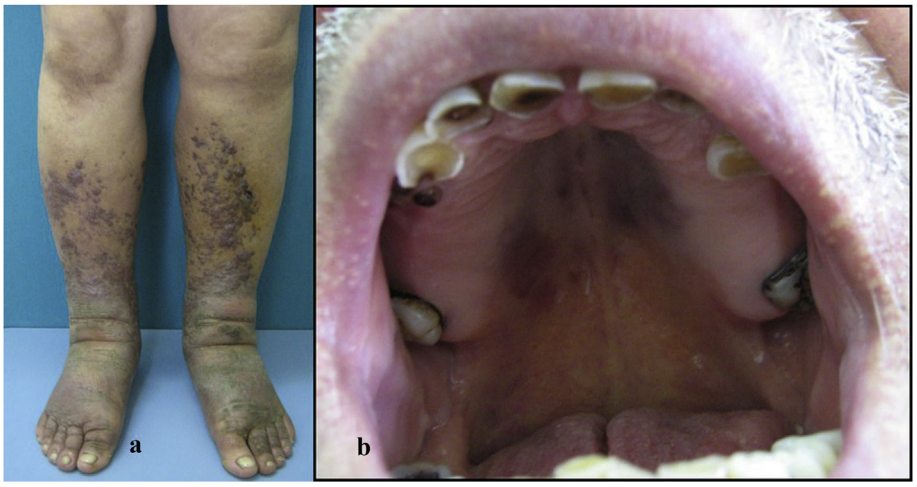

Fig. 2 Different clinical appearances of lesions in classic KS: (a) plague and nodule stage. Clinical lesions consist of violaceous to brown erythematous patches and plaques, most often involving the feet in classic KS. (b) Palatal classic KS.

In the current study, 16 patients (10.3%) were younger than 50 years and the youngest patient was a 35 years old. Classic KS affects men more often than women; our study reported male to female ratio is 2.80. This is perhaps a result of a differential action of sex steroids on the immune system to modify antigen presentation, lymphocyte activation, cytokine and immune cell regulation.[11,12]

In many patients with classic KS, obtaining a complete cure may be an unrealistic expectation, since recurrence rates are high. There are no prospectively randomized trials that compare different treatments for classic KS. Observation without specific treatment is an option for older patients with static disease. Classic KS typically present in the skin of the lower extremities and progresses very slowly. Mucous membranes of the mouth and GI tract and regional lymph nodes may be affected. In our study the most common localization of classic KS was the feet.

Therapies directed at classic KS tumors can be divided into either local and systemic therapies. Management depends on the clinical subtype, although no approach is definitively curative.[13] The published literature on treatment of classic KS consists of retrospective series and case reports. There are no prospectively

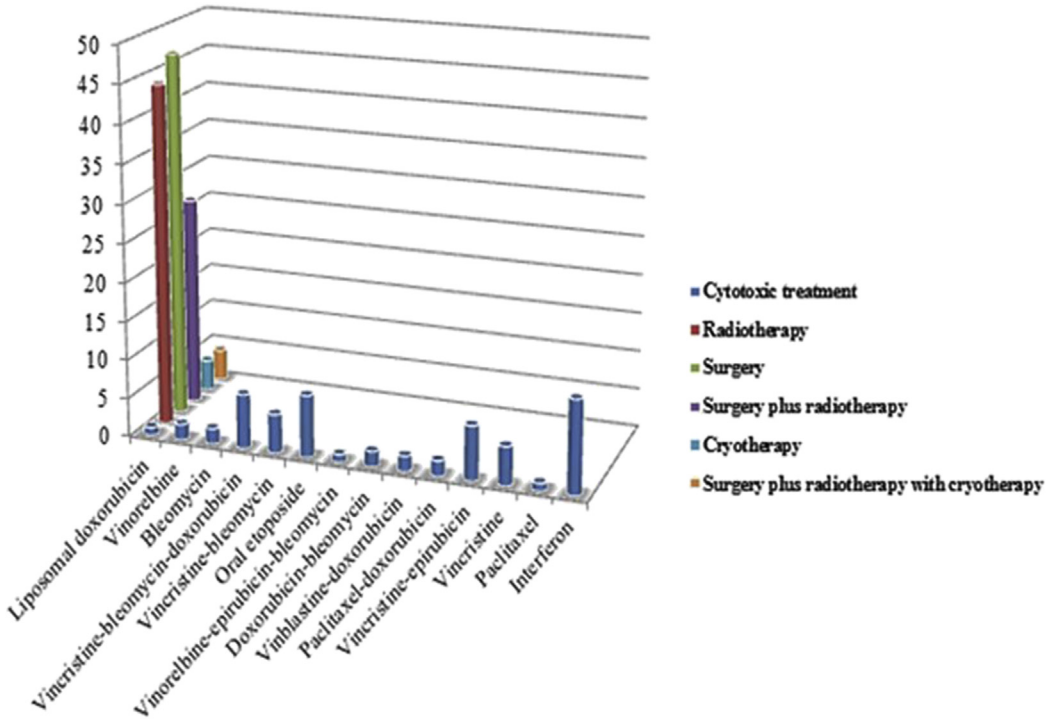

Fig. 3 Local and systemic treatments.

randomized trials that compare different treatments for classic KS. Options for local therapy include surgery, intra-lesional injection of vinblastine, topical retinoid, radiotherapy and cryotherapy. The selection of a local therapy may be influenced by certain factors, such as the extent and location of the lesions and the rapidity of clinical change. Surgery and radiotherapy were the most frequently used treatments in our study. Classic KS are very sensitive to RT. Radiation therapy is a treatment option for the patient presenting with multifocal but relatively localized KS.

Rapidly progressive KS (defined by development of 10 or more new cutaneous lesions per month), pulmonary KS, symptomatic visceral involvement and lymphedema are indications for systemic chemotherapy. Single-agent and combination cytotoxic chemotherapies are most commonly employed for those patients with symptomatic or organ threatening disease who are not candidates for local therapy. Chemotherapy with cytotoxic agents administered singly (etoposide, bleomycin, vincristine) or as part of regimens (doxorubicin–bleomycin–vincristine or vinblastine–bleomycin) have been used in this study.

Combination strategies with either bleomycin and vincristine or doxorubicin, bleomycin, and vincristine initially demonstrated tumor response rates of 57–88%.[14–16] Side effects are more common in combination chemotherapy regimens. These toxicities can be quite debilitating in a patient population on numerous other medications and often dealing with numerous other medical problems. Liposomal doxorubicin achieved responses in 46–58% of patients, compared to 25% with the traditional two-and three-drug combinations.[17–23] We suggest pegylated liposomal doxorubicin (PLD) (20 mg/m^2 every three weeks) as the first-line regimen because of the side effect profiles of these agents are more favorable. There are several options for second-line therapy. The available options include a single-agent taxane, oral etoposide, vinblastine, vinorelbine, or gemcitabine. Eight patients received oral etoposide 50 mg twice daily for 10 days every 3 weeks in our study. Low-dose paclitaxel (100 mg weekly), intravenously proved to be effective and well tolerated in patients with aggressive refractory classic KS, controlling the aggressiveness of the disease.[24] We typically employ liposomal doxorubicin as frontline therapy if there are no contraindications to anthracycline use, and reserve paclitaxel for relapsed disease. Interferon-α is a biological response modifier that has been proven effective as a systemic therapy for KS. There is limited experience with interferon-α in classic KS. Only one of six classic KS patients treated at an IFN-α dose of 3 million units three times a week showed a major response, while four others showed minor (<50 percent) tumor regression.[19] Twelve patients were treated with IFN-α (5 million units subcutaneously three times a week) in our study. This treatment is rarely employed due to the slow onset of action and poor tolerability.

Conclusion

Classic KS arises most commonly in older adult men. It is frequently described as slow-growing, localized disease. Therapeutic choices are often made based upon the experience and medical discipline of the treating clinician. For patients who have a limited-volume disease, we suggest local treatment rather than observation or systemic chemotherapy. There is a need for prospectively defined studies.

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