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Research Article

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What about Non-AIDS Associated Kaposi's Sarcoma? Clinical Features and Efficacy of Chemotherapy: A Monocentric Experience

Khadija Darif*, N Ghozali, Y Sbaiti, M Meliani, M Amziren, FZ EL Mrabet

Medical Oncology Department, Tangier University Hospital Center, Abdelmalek Essaadi University, Tangier, Morocco

***Corresponding Author**
Khadija Darif, Medical Oncology Department, Tangier University Hospital Center, Abdelmalek Essaadi University, Tangier, Morocco.

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Abstract

Background: *Kaposi's sarcoma is a mesenchymal proliferative process of blood and lymphatic system cells. The must well-known risk factors are immunosuppression and human herpes virus. Non-HIV related Kaposi's sarcoma is a rare indolent entity that is more common among people of Mediterranean origin.*

Patients and Methods: *The purpose of this retrospective analysis was to review a series of 21 patients with non-AIDS associated Kaposi's sarcoma who presented to the Department of Oncology at the University Hospital Tangier between 2017 and 2022. Data were extracted from medical records using a pre-established survey sheet. The objective of this work is to define the major clinical features, treatment outcomes, and risk factors of the classic Mediterranean form of the disease in North Africa.*

Results: *Twenty-one patients with non-AIDS associated Kaposi's sarcoma were identified, with ages ranging from 52 to 98 years; the male-to-female ratio was 17:3. All of our patients had the classic form of the disease with negative HIV serology. In 71% of cases, Kaposi's sarcoma was limited to the skin, without lymph node or visceral involvement. The lesions were multiple in all cases, mostly bilateral, and most commonly localized to the skin of the lower extremities. A complete response was achieved in 50% of patients using systemic therapy, and no patients died from Kaposi's sarcoma.*

Conclusion: *Unlike Kaposi's sarcoma in AIDS patients, non-AIDS associated Kaposi's sarcoma from Mediterranean countries is less agressive and more responsive to systemic therapeutic strategies.*

Introduction

Since its discovery, human herpes virus 8 (HHV-8) has been strongly implicated in the pathogenesis of all types of Kaposi's sarcoma, and it is known as Kaposi's sarcoma-associated herpes virus [1]. However, the herpes virus alone is not sufficient for the development of KS. It occurs in a context of immune dysregulation, characterized by CD8+ T cell activation and the production of Th1-type cytokines. This phenomenon explains the angioproliferative process, which, in turn, activates HHV8. Although KS was initially associated with HIV infection, it also occurs in individuals without HIV infection. The classic Mediterranean form was described in 1872 by Moritz Kaposi as rare malignant skin disease that mainly affects elderly men. Other known risk factors besides HHV-8 include immunosuppression, advanced age, diabetes, and corticosteroid medication [1-4]. Four epidemiological forms of Kaposi's sarcoma have been described: AIDS-related, iatrogenic, endemic (most common in sub-Saharan Africa in individuals seronegative for HIV), and classic or Mediterranean form. This study focuses on non-AIDS-related KS in HIV-negative patients presented to the Department of Medical Oncology at University Hospital Tangier between 2017 and 2021.

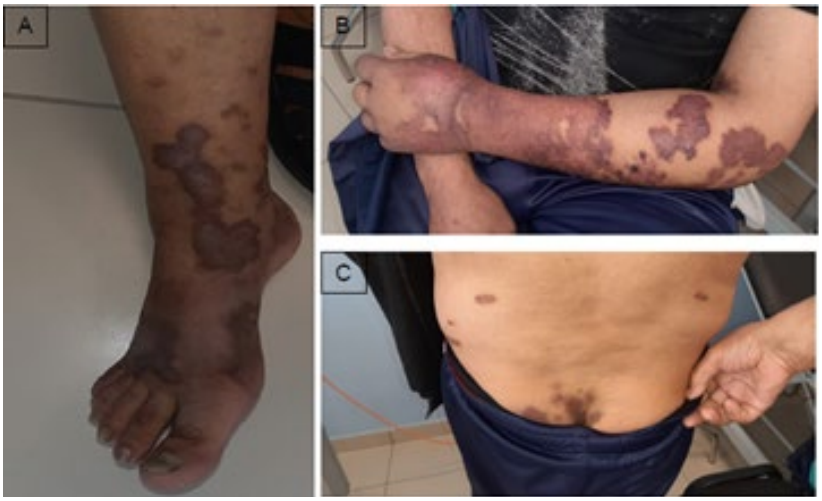

Figure 1: Image showing Multiple Cutaneous Lesions of KS on the Leg (A), Arm (B), and Back (C) in a patient

Materials and Methods

This is a descriptive retrospective study that included a series of 21 patients admitted to the Department of Medical Oncology, University Hospital of Tangier, Morocco. The data for the different patients were collected from medical records on a pre-established survey sheet.

All cases were included according to the following criteria: adults aged 18 or over, with Kaposi's sarcoma lesions on the skin and negative HIV-1/2 screening by macro enzyme immunoassay. Different demographic features such as age and gender of the patient were evaluated, as well as clinical features such as localization and subtype of lesions, metastatic or localized sarcoma, and finally treatment modalities, results, and response evaluation according to the Response evaluation of Kaposi sarcoma defined by the AIDS Clinical Trials Group (ACTG).

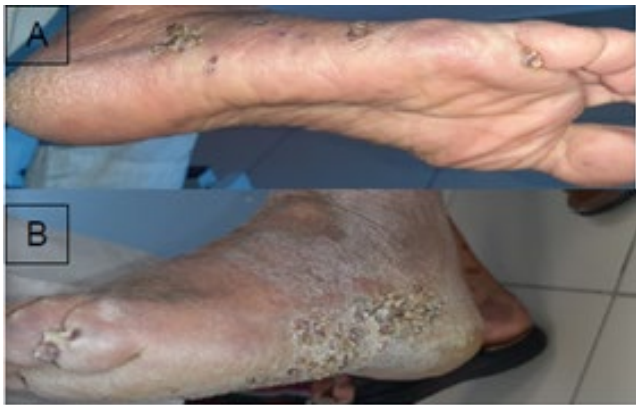

Figure 2: Image showing the Evolution of Left Foot Lesions of KS Before (A) and After 6 Cycles of Paclitaxel (B)

Results

Twenty-one cases of non-AIDS Kaposi's sarcoma were identified in this study. The mean age at diagnosis was 69 years old. The youngest patient was 52 years old, and the oldest developed his classic Kaposi's sarcoma by the age of 96 years old. Male gender was predominant (81%) versus 19% with a sex ratio of M/F of 17/3. All the patients were of Moroccan origin (South-Mediterranean), without any history of immunosuppressive therapy or autoimmune disease. Nevertheless, 18% of patients had chronic diseases such as high blood pressure and diabetes. In 71% (15) of the cases, Kaposi's sarcoma was limited to the skin without mucosal, lymph node, or visceral manifestation; only 29% of patients were metastatic in the lymph nodes (15%) and the lungs (14%). All patients had a classic form with negative HIV serology; KS lesions were multiple in all patients. The most frequent manifestation was the skin of the lower extremities (80%), and 25% of the patients (5) were affected over the entire trunk. All stages of Kaposi's sarcoma lesions were observed within the group, although the most common lesions were irregularly shaped macules and plaques Figure 1.

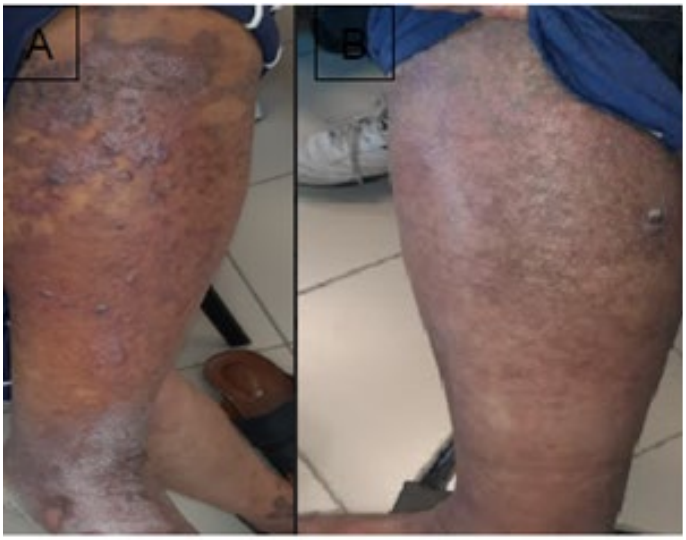

Figure 3: Image displaying the Evolution of Lesions of KS on the Left Leg Before (A) and After (B) 6 cycles of Paclitaxel

Regarding treatment, 67% (14) of patients received chemotherapy, 19% of patients (4) received local treatment based on radiotherapy, surgery, and topical treatment. Three patients were lost to follow-up before starting treatment. In the group that received chemotherapy, paclitaxel was administered in 50% of patients, doxorubicin in 21%, ABV regimen (adriamycin, bleomycin, and vincristine) in 14%, and bleomycin in 14%. Treatment outcome was evaluated according to uniform evaluation, response, and staging criteria (AIDS Clinical Trials Group Oncology Committee). A complete response was achieved in 50% of patients who received first-line treatment; five patients showed disease progression, of whom two received second-line chemotherapy. Third-line chemotherapy was possible in only 14% of patients. There were no disease-related deaths in the group Figure 2 and Figure 3.

Discussion

Non-AIDS Kaposi's sarcoma is considered a rare disease, although its incidence varies according to individual factors such as origin, sex, age, and immune status of the patient [5]. The incidence rates of KS in European population-based registries vary widely and are influenced by factors such as geographic origin, sex, age, and immune status. Low rates have been reported in England and Wales as well as in Denmark, whereas intermediate rates have been reported in Sweden, and higher rates have been reported in Italy [6]. The majority of non-AIDS KS cases in Europe, as reported in a series of 20 patients in Germany, were found in first-generation immigrants from Mediterranean countries with presumably higher incidence rates. Specifically, 12 out of 20 patients in the series were immigrants from Italy and Turkey [5].

Gender is a strong factor that influences the manifestation of Kaposi's sarcoma. Previous male-to-female ratios of 10:1 to 15:1 have been reported in classic Kaposi's sarcoma [7]. Similarly, a Moroccan case cluster showed a significant male predominance, with a male-to-female ratio of 17:3. Age is another factor that influences incidence. The mean age at onset of our 21 patients was 69. In a case series of 874 classic KS patients from 15 Italian Cancer Registries, the mean age was 72 years, which is comparable [6].

Clinically, non-AIDS Kaposi's sarcoma mostly presents as multiple bilateral cutaneous lesions of the lower limb [8]. Hong and Lee compared the characteristics of KS in HIV-positive and -negative subjects and found that HIV status does not affect the occurrence of multiplicity of Kaposi's sarcoma lesions [9]. However, extracutaneous or visceral KS lesions were more likely to occur in HIV-positive patients (p=0.027).

Treatment options for Kaposi's sarcoma include local therapies such as surgery, radiotherapy, and local chemotherapy. From 1987 to 2009, single KS lesions were typically treated through surgical removal and irradiation. Interferon-a-2a has also been used for both systemic and intralesional therapy due to its immune stimulating, antiviral, and anti-proliferative properties [5]. Traditionally, systemic treatment of Kaposi's sarcoma involved several chemotherapeutic agents used either as single agents or in combination. While these treatments can produce reasonable response rates, they typically only provide short-term control [10]. However, these agents have not been extensively tested in large randomized-controlled trials.

For patients with advanced Kaposi's sarcoma, systemic therapy is indicated, and small clinical trials have shown that Taxanes, anthracyclines, microtubule stabilizers, or other chemotherapeutic agents administered alone or in combination can result in response rates ranging from 25 to 88% [11].

The preferred first-line systemic therapy for both limited cutaneous disease and advanced disease is liposomal doxorubicin. In a randomized phase III trial, 258 patients with advanced AIDS-related Kaposi's sarcoma were randomized to receive pegylated-liposomal doxorubicin or doxorubicin/bleomycin/vincristine (ABV) [12]. The over all response rate was 46% (95% CI, 37%–54%) in the pegylated-liposomal doxorubicin arm and 25% (95% CI, 17%–32%) in the doxorubicin/bleomycin/vincristine arm, These results

suggest that pegylated-liposomal doxorubicin may be a more effective first-line systemic therapy for both limited cutaneous disease and advanced disease in patients with AIDS-related Kaposi sarcoma. Response rates for liposomal pegylated doxorubicin range from 71% to 100%, 58% to 90% for vinca-alkaloids, 74% to 76% for etoposide, and 93% for Taxanes [13-17]. The combination of vinblastine and bleomycin was associated with a response rate of 97% [18]. The over all response rate was 46% (95% CI, 37%–54%) in the liposomal doxorubicin arm and 25% (95% CI, 17%–32%) in the ABV arm. Other treatment options for subsequent lines of therapy for relapsed/refractory KS include imatinib, thalidomide, and recently bortezomib, which may also be useful under certain circumstances [19-21].

The response of KS to therapy has been formally defined by the AIDS Clinical Trials Group (ACTG) Oncology Committee and NCCN as follows [22].

- Complete response (CR) is defined as the absence of any detectable residual disease, including tumor-associated (local) edema, persisting for at least 4 weeks. Patients known to have had visceral disease should have restaging with appropriate endoscopic or radiographic procedures relevant to sites involved at baseline.
- Partial response (PR) is defined as no new mucocutaneous lesions, visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions; AND.
- A 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks;
- OR complete flattening of at least 50% of all previously raised lesions (50% of all previously nodular or plaque-like lesions become macules);
- OR a 50% decrease in the sum of the products of the largest perpendicular diameters of at least 5 measurable lesions.
- Stable disease (SD) is defined as any response that does not meet the criteria for progressive disease (PD) or PR. PD is defined as an increase of greater than or equal to 25% in the size of pre-existing lesions and/or the appearance of new lesions or sites of disease and/or a change in the character of the skin or oral lesions from macular to plaque-like or nodular of greater than or equal to 25%. If new or increasing tumor-associated edema or effusion develops, the disease is considered to be progressive.
- Surveillance of patients treated for KS is important, as the disease can recur after an initial complete response.

Conclusion

In conclusion, this study provides valuable insights into the clinical manifestations, treatment approaches, and outcomes of patients with non-AIDS associated Kaposi sarcoma. With the emergence of new treatments based on a better understanding of the carcinogenesis process, there is hope for even better outcomes in the future. While several chemotherapeutic agents have proven effective in controlling KS, the overall survival of patients with Kaposi sarcoma has improved significantly, and long-term survival has become a realistic goal for many patients. Nonetheless, continued surveillance of patients treated for Kaposi sarcoma is crucial, as the disease can recur even after an initial complete response. Overall, this study underscores the importance of early detection, prompt treatment, and ongoing care to maximize the chances of long-term survival and improved quality of life for patients with Kaposi sarcoma.

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