ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Sep 25; 6(9):1688-1693.
https://doi.org/10.3889/oamjms.2018.354
eISSN: 1857-9655
Case Report

A Series of Patients with Kaposi Sarcoma (Mediterranean/Classical Type): Case Presentations and Short Update on Pathogenesis and Treatment

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Citation: Temelkova I, Tronnier M, Terziev I, Wollina U, Lozev I, Goldust M, Tchernev G. A Series of Patients with Kaposi Sarcoma (Mediterranean/Classical Type): Case Presentations and Short Update on Pathogenesis and Treatment. Open Access Maced J Med Sci. 2018 Sep 25; 6(9):1688-1693. https://doi.org/10.3889/oamjms.2018.354

Keywords: Kaposi; Pseudo-Kaposi; Stewart Treves syndrome; Radiation therapy; Treatment choice; Morbus Mali

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Received: 26-Aug-2018; **Revised:** 30-Aug-2018; **Accepted:** 01-Sep-2018; **Online first:** 20-Sep-2018

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Kaposi's sarcoma was first described in 1872 by Moritz Kaposi. To date, it is considered a malignant disease is originating from the endothelial cells of the lymphatic vessels believed to be infected with HHV-8. The current classification defines four major epidemiological forms of Kaposi's sarcoma: classical, endemic, AIDS-associated, and iatrogenic.

CASE REPORT: A 90-year-old male is presented with multiple plaques- and tumour-shaped brown-violet formations located on an erythematous-livid base in the area of both feet and both shanks. Two samples were taken from the lesions on the skin of the shanks, with histopathological examination and the subsequent immunohistochemistry showing Kaposi's sarcoma.

CONCLUSIONS: Kaposi sarcoma is a disease that causes difficulties both in diagnostic and therapeutic respect. The only sure way to determine the correct diagnosis is immunohistochemical staining with the anti-HHV8 antibody. Despite the wide range of systematic and local treatment options, there is still no unified algorithm and a unified strategy for the treatment of Kaposi's sarcoma.

Introduction

Kaposi's sarcoma is a tumour originating from endothelial cells where there is a suspected infection with human herpesvirus-8 (HHV-8) [1]. It is the most common malignancy among the AIDS patients [2]. The clinical picture and the standard histology are not always sufficient for Kaposi's sarcoma to be as precise as possible distinguished from some other diseases [3]. In these cases, the conduct of an immunohistochemical study to determine the correct diagnosis is of paramount importance [4].

Five major subtypes of Kaposi's sarcoma can be differentiated: (1) classical type of predominantly older Caucasian males; (2) endemic Kaposi's sarcoma of the Sub-Sahara region, which is not HIV-associated; (3) transplantation- and immunosuppression-associated type; (4) AIDS-related type; (5) classical type in HIV-positive patients.

There is still no established golden standard in the treatment of Kaposi's sarcoma, but there are some therapeutic options that show complete or partial remissions [5].

Case Report 1

A 90-year-old man is presented at the Department of Dermatology and Dermatologic Surgery at the Medical Institute of Ministry of Interior, (MVR-Sofia), Bulgaria, who suffers from chronic venous insufficiency and benign prostatic hyperplasia. The patient was hospitalised due to the presence of multiple plaque-shaped to tumour-shaped formations in the area of the left leg. The lesions date back to approx. 2 years, due to which lesions the patient had two previous hospitalisations in other health institutions and conducted antibiotic and corticosteroid therapy without success. During the dermatological examination, in the area of both feet and the two shanks, the presence of brown-violet tumor-shaped formations was found with a diameter of 0.5 to 2.0 cm, located on an erythematous-livid base (Figure 1a, 1b and 1c).

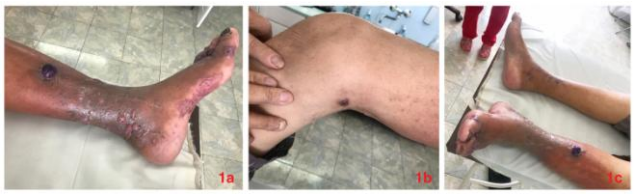

Figure 1: a), b) and c) - Kaposi sarcoma lesions on the left and right lower extremities-presence of nodules, blisters and hyperpigmentation

The left-sided pathological changes were clinically more pronounced (Figure 1a). The available clinical picture was suspected for Kaposi's sarcoma. Samples were taken of the tumour-shaped formations, on the skin of both shanks for histological verification of the diagnosis determined.

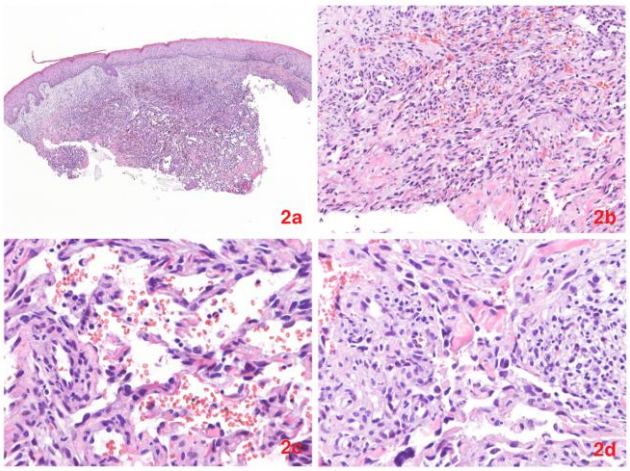

Figure 2: Kaposi sarcoma. Histopathology (H&E); a) Under a slight acanthotic epidermis vascular tumour with partially high cellularity (x40); b) Atypical spindle cells with small slit-like vascular spaces. Preexisting vessels are in part surrounding by spindle cells, this way appearing freely floating, so-called promontory sign (x100); c) Vascular lining by atypical, in part hyperchromatic spindle cells. Extravasated red blood cells (x400); d) In part additional plasma cells in the infiltrate (x400)

The histopathological examination and subsequent immunohistochemistry showed definite evidence of Kaposi's sarcoma (Figures 2a, 2b, 2c, 2d, 3a, 3b, 4a, 4b and 4c).

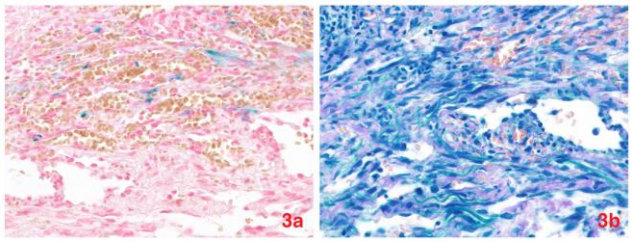

Figure 3: Kaposi sarcoma histopathology - a) among tumour cells hemosiderin deposits; b) many extravasated red blood cells

The ultrasound examination performed on the lower extremities revealed the presence of enlarged and pathologically changed lymph nodes in the left femoral triangle.

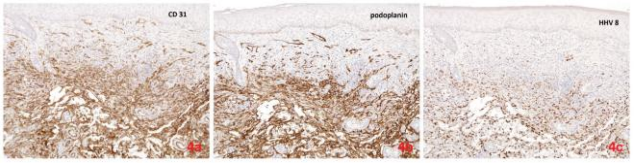

Figure 4: Kaposi sarcoma-immunohistochemistry - a), b) and c) Tumor cells are labelled with antibodies against CD31, podoplanin, and HHV8

Systemic therapy with Ceftriaxone was performed 2 g x 1/day IV for 7 days, and the local therapy included daily iodasept ointment dressings for 7 days. Nadroparin calcium was prophylactically applied 0.4 x 1/day SC for 7 days. As a result of the conducted treatment, lymph node subsiding was observed, and the patient was redirected to perform radiation therapy at a specialised oncology centre.

Case Report 2

A 76-year-old male patient presented with several nodules on his left forefoot and lower leg which developed during the last 6 months. He reported burning and pain sensations on the ulcerated lesions located on the 2nd and 3rd left toe. His medical history was remarkable for prostate cancer, nephrectomy because of a cirrhotic kidney and a first-grade atrioventricular block. On examination, we observed multiple livid or soft brownish nodules on the left lower leg and forefoot with ulcerations on the toes. Enlarged lymph nodes were palpable in both groins.

A skin biopsy was taken for histopathology. Within the dermis, bizarre formed; partly ectatic blood vessels with prominent endothelial and positive promontories sign, extravasation of red blood cells

and siderophages were noted. The vascular parts within papillary bodies showed a spindle cell type. Endothelial were positive for CD31, podoplanin, and HHV-8 and partially for CMYK by immunohistochemistry. The mitotic rate was about 10 to 20% with Ki67-staining. Diagnosis: Classical KS is shifting from patch to plaque stage.Laboratory findings: Lymphopenia of 12% (normal range: 25-45%), erythrocytes 4.29 (4.6-6.2Tpt/l), Hb 7.9 (8.6-12.1mmol/l), ß-2-microglobulin 2.6 (0.8-2.2mg/l), CD3+/CD4+-T-helper cells 79.8 (35-66%), CD3+/CD8+-T-suppressor cells 11.1 (17-46%), ratio helper/ suppressor cells 7.19 (1.0-2.3), HIV test negative. Imaging: Computerized tomography demonstrated a pulmonary nodule of 0.5cm in diameter dorsobasilar on his right side. Several Hilary and pulmonary lymph nodes with a diameter < 1 cm. Ultrasound abdomen/ groins: Tumor-like growth in the left groin and an atypical lymph node (19 mm). MRI of the head excluded any tumour spread. The patient was referred to the Department of Radiology for radiotherapy.

Figure 5: Case #2: a) Nodules on the lower left leg and foot. Left Lower leg with patches and plaques of classical KS; b) Immunostaining for CD31; c) Immunostaining for CD34; d) Immunostaining for HHV-8

Discussion

Kaposi's sarcoma (KS) was first described in 1872 in an article titled "Idiopathic multiple pigmented sarcoma of the skin" by Moritz Kaposi and to this day is named after him [6]. Tommaso de Amicis-an Italian dermatologist, confirmed his findings, albeit ten years later [7]. In 1981, Alvin Friedman-Kein changed the perceptions that KS is a rare disease affecting predominantly senior men and gives a whole new perspective by concluding that Kaposi's sarcoma can be HIV-associated [8]. The subsequent epidemiological studies in people with AIDS revealed two important features of this disease, namely that it is possible to be sexually transmitted as is HIV, on the one hand, and on the other, immunosuppression promotes the development of Kaposi's sarcoma [2].

Still, the genesis of this type of sarcoma is not fully elucidated [9]. Currently, the leading theory is that Kaposi's sarcoma is a tumour originating from the endothelium of the blood vessels that are most commonly associated with Kaposi's sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) infection [1] [10] [11]. It is believed that it is this virus that is the cause of a change in the differentiation and the function of the endothelial cells, resulting in the appearance of altered vascular structures to a lymphatic phenotype and determining the angioproliferative character of KS [1] [12]. A possible explanation for this mechanism is that this occurs with the involvement of VEGFR3-lymphatic endothelial-cell-specific receptor important for lymphangiogenesis [12]. It is considered that the transcription factor Its-1 activates the promoter of VEGFR3 and thus he plays a role in KSHV activation of endothelial cells during latent KSHV infection [12]. It is Its-1 that is considered to be the regulator involved in the induction of angiogenic phenotypes by KSHV [12]. As a rule, this type of sarcoma includes four types of forms: classical, African (endemic), AIDS-associated (epidemic) and iatrogenic (organ transplant-related) form [10] (Table 1). There is also another form of Kaposi-the so-called lymphadenopathic Kaposi's sarcoma, which can occur in people with AIDS but also in immunocompetent children or adults [13] [14] [15]. It affects the lymph nodes, the internal organs, the gastrointestinal tract and it can pass into a disseminated form with an aggressive course of progression [15].

Table 1: Variants of Kaposi's sarcoma

Variant	Risk Group	Median survival
Classic	Senior men of Eastern European or Mediterranean origin	Years or decades
Endemic	African children and adults	Months or years
Immunosuppression-associated, or transplantation-associated	Organ transplant recipients	Months or years
AIDS-associated	Persons infected with human immunodeficiency virus, especially homosexual or bisexual men	Weeks or months
Classical KS in HIV-positive patients	HIV-positive younger patients	Months or years

Usually, the lesions of Kaposi's sarcoma go through three stages: 1) early with the appearance of macules (patch stage), 2) followed by the appearance of plaques (plaque stage), and finally, 3) nodules (tumour stage) [10] [11] [16]. At the same time, there is also data in the literature for more specific histological variants that include anaplastic, hyperkeratotic, lymphangioma-like, bullous, telangiectatic, ecchymotic, keloidal, pyogenic granuloma-like, micronodular, intravascular, glomeruloid and pigmented KS, KS with sarcoid-like granulomas and KS with myoid nodules [10] [11].

In a historical aspect, Kaposi's sarcoma is described as a disease primarily affecting men of Mediterranean origin, as our patient, with a pre-target location, the lower limbs and slow progression [17].

Risk factors associated with KS include male gender, HLA-DR5 genetic marker, homosexuality, immunosuppression and viral agents such as Cytomegalovirus [17]. It is believed that in patients with HIV infection, KS may occur at any time, most commonly when CD4 count < 200 cells/mm^3 [14]. For this reason, their number is used as a prognostic factor for the evolution of Kaposi's sarcoma, and CD4 count > 200/mm^3 and only cutaneous involvement [18] is considered to be a good prognosis. Thus, the immunosuppression after organ transplantation or in AIDS can form the two groups of patients at highest risk and incidence of Kaposi's sarcoma [2] [19].

Histopathological, the Kaposi's sarcoma is characterised by the presence of hyaline bodies, deposits of hemosiderin, spindle cell and the formation of vascular channels between spindle cells [3] [16]. It is these features that determine the range of diseases that should be considered in a differential diagnosis-granuloma pyogenicum, leiomyoma, leiomyosarcoma or fibrosarcoma [3]. Besides these, a diagnostic error can also occur with dermatofibroma, hemangioma or scar [20]. Difficulties may also result from the localization of KS [21]. Although it is typical that the lymph nodes and the visceral organs are affected, an atypical clinical manifestation is also possible, covering other anatomical areas such as the musculoskeletal system, central and peripheral nervous system, larynx, eye, major salivary glands, endocrine organs, heart, thoracic duct, urinary system, breast, sites of previous iatrogenic trauma (wounds) and blood clots is also presented [21].

The performance of immunohistochemistry and immunohistochemical reactivity for CD31, CD34, D2-40 and FLI1 [4] [22], is of crucial importance for determining the diagnosis. The results of the immunohistochemistry and the sensitivity for these markers were found to be the same in AIDS-related and non-AIDS-related KS, as well as between the nodular-and patch/plaque-stage KS [22]. Furthermore, due to the possibility of a lymphangioma-like Kaposi's sarcoma and the existing risk of an incorrect diagnosis of lymphangioendothelioma, it is important to perform immunohistochemical staining with anti-HHV8 antibody [23]. The same also applies to conditions with chronic lymphoedema when KS can be mistaken with the Stewart-Treves Syndrome (STS) [24]. The difference between them is that KS does not necessarily require the presence of lymphedema for its development and is etiologically associated with a viral infection that is lacking in STS [25].

Difficulties in the clinical diagnosis are often also created in the cases of pseudo-Kaposi's sarcoma-acroangiodermatitis, and again only the HHV-8 study can distinguish it from KS [26].

Cutaneous angiosarcoma (CAS) is another interesting tumour that also has a vascular origin and should be distinguished from Kaposi sarcoma [27]. It is believed that programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) expression by tumour cells play a key role in the angiosarcoma pathogenesis [27]. However, there are cases in which 1) angiosarcoma can detect PD-L1 negativity in immunohistochemistry, 2) even more interesting- to be affected by PD-1 inhibitor therapy with pembrolizumab despite this negativity and 3) when it comes to lesions of vascular origin a guarantee for confirmation or exclusion of Kaposi's sarcoma diagnosis is only HHV- 8 positivity [23] [27].

Currently, a wide range of options is used for treatment of Kaposi's sarcoma that include chemotherapy, radiotherapy, immunotherapy, cytotoxic agents, liposomal anthracyclines, paclitaxel, retinoic acids, pazopanib as well as some antiangiogenic agents such as AGM 1470 (TNP 470), thalidomide and glutamine disodium (IM 862), that show promising results [5] [28]. Self-administered or in combination, the chemotherapeutic agents provide acceptable results, but recurrences of KS occur frequently, and the progression-free periods are often short [29].

For classical KS, which is radiosensitive, the radiotherapy is of key importance in the therapy of all forms. It has the greatest effect in the early stages of the disease [30] [31]. However, as it reduces the pain, oedema and ensures control of the bleeding, radiotherapy can also be used as a palliative treatment in advanced cases of KS [31] [32]. In this regard, doses of 15.2 Gy for oral lesions and 20 Gy for lesions involving conjunctiva, eyelids, lips, hands, feet, penis, and anal region provide good control of the symptoms [33]. For the other parts of the body, a dose of 30 Gy may be used, with the hypofractioning showing the best outcome regarding recurrence-free survival, the toxicity and the local control [34]. In non-AIDS associated KS (NAKS), radiotherapy provides a very good therapeutic control [34].

For patients with AIDS-related Kaposi's sarcoma, however, the first line of treatment is the high-activity antiretroviral therapy (HAART) [5]. There is evidence that even a self-administered HAART therapy may lead to spontaneous regression of KS in AIDS patients [35]. The spontaneous regression is described in the literature and discontinuation of immunosuppressive treatment in the iatrogenic form of KS after transplantation [36]. More surprising in this respect is the data from a documented partial regression in cases of non-HIV, non-iatrogenic Kaposi sarcoma [37]. The precise mechanisms under which this is done are still within the hypothetical sphere [37].

The WHO has developed international guidelines for HIV-associated KS, but there is still no standardised approach to the treatment of other types of Kaposi's sarcoma [5] [38].

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