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A clinical case of an immunosuppressive generalized form of Kaposi's sarcoma in a patient with pemphigus vulgaris

Evelina Koldarova[1], Bahrambek Mukhamedov[2], Aziz Aliev[3]

[1]Dermatology Department, Republican Specialized Scientific and Practical Medical Center of Dermatovenereology and Cosmetology, Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan
[2]Dermatology Department, Tashkent State Dental Institute, Tashkent, Uzbekistan
[3]Department of Dermatovenereology, Tashkent Medical Academy, Tashkent, Uzbekistan

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Corresponding author:
Evelina Koldarova.
E-mail: koldarova7@gmail.com;
ORCID: 0000-0001-9450-4004

Abstract

The article presents the literature data on Kaposi's sarcoma a lymphangioproliferative neoplasia induced by the Herpes Virus type 8. The main forms, clinical manifestations and treatment are described. A clinical case of the development of an immunosuppressive generalized form of Kaposi's sarcoma induced by glucocorticosteroid therapy in a patient with pemphigus vulgaris is presented. With this clinical example, it is important to emphasize the potential risk of Kaposi's sarcoma on the background of secondary immunosuppression. Immunosuppressive Kaposi's sarcoma (iatrogenic type) is most often associated with long-term use of immunosuppressive therapy in transplantation organs and in patients receiving immunosuppressive therapy for autoimmune diseases, which leads to an increased risk of developing Kaposi's sarcoma by 150-1000 times compared with the general population. The ratio of men and women with this type is 2:1, while with the idiopathic (classical) - 17:1. Reliable diagnosis of the disease is necessary, based on a combination of history data, clinical and histological patterns of the pathological process, as well as additional laboratory markers, which will allow timely determination of further patient management tactics and, accordingly, provide a more favorable prognosis for the course of the disease.

Key words: Kaposi's sarcoma, HHV type 8, clinical case, secondary immunosuppression

Introduction

Kaposi's sarcoma (KS) is a systemic multifocal tumor of endothelial origin with a primary lesion of the skin, lymph nodes, and internal organs [1]. KS was first reported in 1872 by the Austro-Hungarian dermatologist Moritz Kaposi under the name "idiopathic multiple pigmented sarcoma" in elderly European men with multiple cutaneous and extracutaneous neoplasms, all of whom died within 2 years. In 1898, G. Koebner proposed the term "Kaposi's sarcoma" after the name of the discoverer of the disease [2]. The development of Kaposi's sarcoma is most likely in individuals belonging to the following risk groups: men of Mediterranean origin over 60 years old, a number of Central African countries, HIV-infected men, transplant recipients or patients receiving long-term immunosuppressive therapy [3]. Men get sick 9-15 times more often than women.

Currently, 4 variants of KS are distinguished, which have peculiar epidemiological characteristics and clinical course, but have comparable histopathological features [4,5]:

1. Classical (idiopathic, sporadic) KS is common among elderly men of Mediterranean or Jewish descent and, unlike the cases originally described by Kaposi, usually has a sluggish, protracted clinical course and

primarily affects the skin on the legs. As a rule, it begins as a localized reactive inflammatory-angiogenic process of the skin and can slowly progress to a real sarcoma, in rare cases with damage to internal organs [5].

2. Endemic (African) SK - common in some countries of Central Africa. There is a chronic type, which does not differ from the classical form, and a rapidly progressing lymph adenoid-like variant, characteristic of childhood, with a fatal outcome 2–3 months after the onset of the disease [6].

3. Immunosuppressive (iatrogenic) SK, which develops under the influence of immunosuppressive therapy of various origins, most often occurs after transplantation of various organs [7].

4. Epidemic (AIDS-associated) SK - rapidly progressing in HIV-positive patients, characterized by the early formation of extracutaneous lesions.

According to the literature, there is currently no consensus on the pathogenesis of KS. The origin of spindle cells from the endothelium of lymphatic vessels is considered [8]. However, the lymphatic or vascular nature of these cells is still a matter of debate. Indeed, spindle cells express both vascular and lymphatic endothelial cell markers (VEGF-3, LYVE-1 and podoplanin or CD34, CD31 and CD36, respectively) and have the phenotypic characteristics of two cells. The cause of KS was not known until 1994, on the basis of epidemiological assumptions an infectious origin independent of HIV was proposed, a directed search led to the discovery of human herpes virus type 8 (HHV-8). The HHV-8 genome is found in all elements of the SC in a latent form, at all stages of the disease, regardless of the clinical variant, however, a small proportion of viral particles (<5%) is in a replicative state and, as reported, is potentially involved in the proliferation of neighboring cells, which suggests that they play a crucial role in the process of oncogenesis [9]. The immune response to HHV-8 paradoxically exacerbates the reactive process, contributing to the transition to true sarcoma. In the classical form of KS, there is no change in the specific acquired immunodeficiency in both T-cell populations, while in the non-classical form of KS, initiation and progression are modulated in the immune system [10].

The predominant localization of foci of rashes is the lateral surfaces of the legs, feet, and hands. The lesions are usually symmetrical, with clear boundaries. Subjectively, an asymptomatic course is more often characteristic, sometimes itching and burning are possible. There are 3 clinical stages of KS:

1. Spotted - reddish-cyanotic or reddish-brown spots, 1-5 mm in diameter, irregular in shape, with a smooth surface, asymmetrically or symmetrically arranged [11,12]. Considered as an early stage, characterized by slow horizontal and vertical growth, with a tendency to progress to hard plaques and occasionally to nodules.

2. At the papular stage - the presence of papules of a spherical or hemispherical shape, densely elastic consistency, 0.2-1 cm in diameter is noted. Papules tend to group into plaques with a smooth or rough orange-peel surface, sometimes with papillomatous growths [13].

3. Tumor stage - characterized by the formation of single or multiple nodes up to 1-5 cm in diameter, soft or densely elastic consistency, with a tendency to merge and ulcerate [14]. Edema often occurs around the tumor, accompanied by the formation of depressions when pressed. Such edema can transform into fibrosis. The color of the lesions changes to brownish, hyperkeratosis of the proper skin develops, and ulceration develops, especially on the lower extremities. Ulcers are deep, irregularly shaped, with twisted edges, bluish in color and tuberous, bloody-gangrenous bottom, sharply painful. After several years of progression, the spread of KS to other parts of the body is often detected and tumors can be found on the mucous membranes of various organs, including the oral cavity and/or genitals. There are also lesions of the internal organs, respiratory organs, lymph nodes [9,14], where they rarely manifest any symptoms [3].

The course of KS can be acute, subacute and chronic. Life expectancy is from 2 months up to 2 years [4].

The histopathological picture depends on the stage of KS development. Early patchy elements are characterized by an increase in the number of vessels in the surface layer of the dermis, surrounded by irregularly shaped endothelial cells. Vessels run parallel to the surface of the skin, are often tortuous and can form bizarre cracks and fissures. In the adjacent skin, areas of hemosiderin deposition and extravasal erythrocytes, as well as a moderate inflammatory infiltrate, are often detected. In the plaque stage of KS, marked vascular proliferation is noted in all layers of the dermis with multiple dilated and angular vessels that traverse collagen. The nodular foci of KSs consist mainly of spindle-shaped cells arranged in the form of fibers and alternating bundles with disordered uneven slit-like vascular zones without endothelial lining. More developed elements may show pronounced pleomorphism, nuclear atypia, and mitotic figures. Along the periphery of solid tumors, lymphangiomatous areas with bizarre vascular lumens, intra and extravascular erythrocytes, and siderophages can be found. A moderate inflammatory infiltrate consisting of lymphocytes, histiocytes, plasma cells, and, rarely, neutrophils is almost always detected at all stages of KS [3].

The main goals of treatment are to prevent disease progression, reduce swelling and, prevent organ damage, and relieve psychological stress. Therapy for KS should be selected depending on the subtype, stage of the disease, and taking into account the immune status of the patient [15]. With regard to the herpes virus, there is no eradication treatment for HHV-8. This fact makes scientists doubt the possibility of curing any form of KS. Targets in the treatment of KS are also HIV (in patients with an AIDS-associated form of the tumor), the processes of angiogenesis and cell differentiation. Local methods of treatment include: surgical treatment, liquid nitrogen destruction, topical therapy using 9-cis-retinoic acid, imiquimod [16], interferon, local chemotherapy [3]. The method of photodynamic therapy (PDT) [17] is also used, which is minimally invasive, has a high selective activity of tumor lesions, low toxicity, and no risk of severe local and systemic complications. The most commonly used prospidin, which is characterized by high tropism to the skin and no ambivalent effect after withdrawal, hemotoxic effect [8,18]. Depending on the immune status of the patient, interferon 2, carbamoylaziridine, IFN-α, IL-12, etc. are additionally used during prospidin therapy [18]. It is assumed that they cause apoptosis of SC cells [19]. In patients with rapidly progressive or advanced classical KS, especially with involvement of internal organs, chemotherapeutic agents are widely used as monotherapy or combined treatment [3].

Case presentation

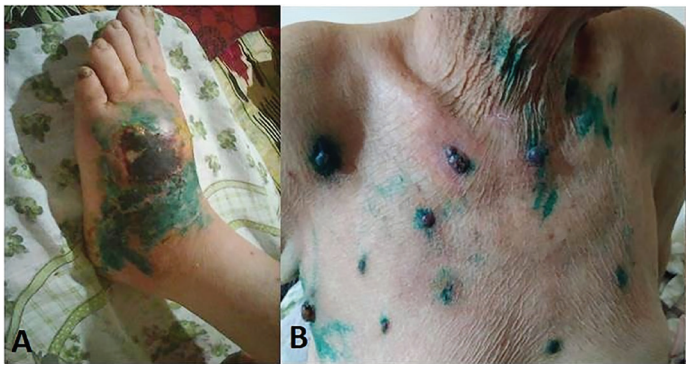
We present our clinical observation of the development of an immunosuppressive generalized form of Kaposi's sarcoma in a patient with pemphigus vulgaris. Patient S., 73 years old, who received regular inpatient treatment for pemphigus vulgaris for 6 years, was discharged after another hospitalization on 11 tablets

(55 mg/day) of prednisolone with gradual dose titration. With a decrease in the dose of prednisolone to 20 mg/day, he noted the appearance of rashes on the left foot, swelling and soreness. He was examined by a surgeon at the place of residence, where an incision was made with suspicion of phlegmon. From the words, no signs of phlegmonous inflammation were detected. After 1-week, purple spots began to appear on both legs, gradually increasing in size. After 1-month, similar rashes appeared on the body, soreness, weakness, inability to move independently, in connection with which the patient turned to the Republican Dermatovenerological Clinical Hospital of the Ministry of Health of the Republic of Uzbekistan.

Status preasens: General condition of moderate severity. The patient is lying down, does not move independently. Normosthenic body type. On auscultation in the lungs, hard breathing, single wheezing is heard. The borders of the heart are deviated to the left. Stool - there is a tendency to constipation.

Status localis: The skin pathological process is widespread, symmetrical, chronic inflammatory. Localized on the skin of the lower and upper extremities, the anterior and posterior surface of the body. The elements of the lesion are represented by papules, plaques, nodes from 1 to 5 cm in diameter, bluish-red color, hemispherical shape with sharp borders, rounded outlines, in some places covered with a small amount of scales. Their surface is uneven, bumpy. The lower extremities are edematous, the skin is infiltrated. On the feet there are nodes of a bluish-purple hue, with an ulcerated surface, multiple erosions, ulcers with purulent discharge. There is a specific putrid smell. Visible mucous membranes are free from rashes. Subjectively, the patient is concerned about moderate pain in the area of the rash. Rashes that speak for pemphigus in the patient were not observed (Figure 1).

Figure 1 - A) Patient C. Nodules of a bluish-purple color with an ulcerated surface, multiple erosions, ulcers with purulent discharge. B) On the skin of the body - papules, plaques, nodes of bluish-red color from 1 to 5 cm in diameter, hemispherical in shape with sharp boundaries

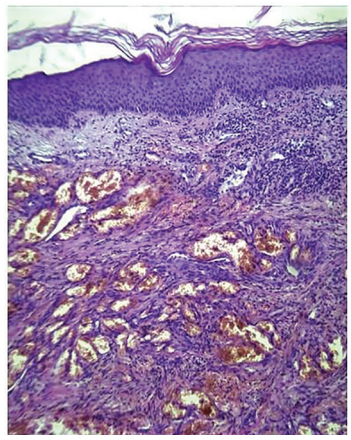


According to clinical and laboratory data: Hypochromic anemia was detected in the KLA; In OAM - traces of protein, salts of uric acid. Biochemical analysis of blood - no pathology. HIV test is negative. In the immunogram, there is a decrease in the relative and absolute values of the total pool of T-lymphocytes, an imbalance in the immunoregulatory populations of T-lymphocytes. IRI is suppressed. Increased the number of natural killers. SD level 4 - 315 (N-580-1110).

To clarify the clinical diagnosis, with the consent of the patient, a diagnostic skin biopsy was performed from the lesion in the shin area.

Histological examination of the skin: A slight hyperkeratosis was revealed, in some places detachment of the stratum corneum. Slight acanthosis, granular layer without features. In the dermis, chaotic proliferates of slit-like and wide-lumen capillaries are noted, represented by atypical thin-walled vessels. In the middle third of the dermis, there is an accumulation of spindle-shaped cells, hemosiderin deposition, collagen fibers are fibrously changed in places. Skin appendages are not defined (Figure 2). Conclusion: Kaposi's sarcoma, angiomatous type.

Figure 2 - Histological picture of a biopsy specimen from the skin of the body, stained with Hematoxylin-eosin. Zoom x 100



Based on complaints, anamnesis (long-term use of corticosteroids), the result of a biopsy, the diagnosis was made: Kaposi's sarcoma, a generalized form of the immunosuppressive type. After making the final diagnosis and consulting an oncologist, he was transferred to the Republican Oncology Center for further treatment. However, 5 months later, against the background of the progression of the process, the patient died.

Conclusion

Thus, taking into account the literature data, the immunosuppressive type of SC can occur with prolonged use of GCS, which is not excluded in our patient, and the trigger for the rapid progression of the process may have been surgical manipulation, after which, according to the patient, bluish spots began to appear literally every day on the legs, and then gradually all over the body. Interest in the study of MC, despite the fact that it was described more than 140 years ago, is associated with an increase in the incidence of this disease, including against the background of HIV infection, immunosuppressive therapy for chronic systemic diseases, organ and tissue transplantation. However, the lack of efficiency in diagnosing and treating various types and forms of KS, the lack of consideration of the stage of the disease, the prevalence of the pathological process, the degree of immunosuppression, the severity of side effects from the therapy, makes this disease a serious interdisciplinary problem at the moment, which is faced not only by dermatologists, oncologists, rheumatologists, but also doctors of other specialties. With an integrated approach to the diagnosis and treatment of SC, it is possible to effectively control the tumor process, which makes it possible to achieve a sufficiently long remission, and in some cases, a complete regression of the pathological process.

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References

1. Aboulafia D.M. Kaposi's sarcoma. *Clin. Dermatol.* 2001; 19(3):269-283. https://doi.org/10.1016/S0738-081X(01)00176-6
2. Kalamkaryan A. A., Mordovtsev V. N., Trofimova L. Ya. Clinical dermatology. Rare and atypical dermatoses (Klinicheskaya dermatologiya. Redkiye i atipichnyye dermatozy) [in Russian]. Erevan: *Ayastan*. 1989; 461–471.
3. L.A. Goldsmith, S.I. Katz, B.A. Gilcrest et al. Fitzpatrick's dermatology in clinical practice: in 3 volumes (Dermatologiya Fitspatrika v klinicheskoy praktike v 3 t.) [in Russian]. Moscow: *Panfilova*. 2016; 2:1216.
4. Lectures on clinical oncology. Textbook under the total. ed. G.V. Bondar and S.V. Antipova - Donetsk: PP "Kalmius". 2009. 588 p. [in Russian].
5. Schwartz RA. Kaposi's sarcoma: an update. *J. Surg. Oncol.* 2004; 87(3):146-151. https://doi.org/10.1002/jso.20090
6. Kaplan L.D. Human herpesvirus-8: Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. In: Am. Soc. Hematol. Educ. Program, 2013. *Hematol*. 2013; 1:103-108. https://doi.org/10.1182/asheducation-2013.1.103
7. Barozzi P., Bonini C., Potenza L. et al. Changes in the immune responses against human herpesvirus-8 in the disease course of posttransplant Kaposi sarcoma. *Transplantation*. 2008; 86(5):738-744. https://doi.org/10.1097/TP.0b013e318184112c
8. Martellotta F., Berretta M., Vaccher E. et al. AIDS – related Kaposi's sarcoma: state of the art and therapeutic strategies. *Curr. HIV Res.* 2009; 7(6):634-638. https://doi.org/10.2174/157016209789973619
9. Cinelli R., Vaccher E., Tirclli U. Clinical features and management of Kaposi's sarcoma. In: Volberding P.A., Palevsky J.M., Walsh C.C., eds. Viral and immunological malignancies. Hamilton: BC *Decker Inc.* 2006. p.9-107.
10. Brown E.E., Whitby D., Vitale F. et al. Virologic, hematologic, and immunologic risk factors for classic Kaposi sarcoma. *Cancer*. 2006; 107(9):2282-2290. https://doi.org/10.1002/cncr.22236
11. Iscovish J., Boffctta P., Franceschi S. et al. Classic Kaposi sarcoma: Epidemiology and risk factors. *Cancer*. 2000; 88(3):500-517. https://doi.org/10.1002/(SICI)1097-0142(20000201)88:3<500::AID-CNCR3>3.0.CO;2-9
12. Martin J.N. Epidemiology of Kaposi's sarcoma – associated herpesvirus infection. In: P.A. Volberding, J.M. Palevsky, C.C. Walsh, eds. Viral and immunological malignancies. Hamilton: BC *Decker Inc.* 2006. p.67-88.
13. A. Sh. Aliev, B.I. Muhamedov, E.V. Koldarova. On the issue of differential diagnosis of pseudosarcoma and Kaposi's sarcoma (clinical case) (K voprosu o differentsial'noy diagnostike psevdosarkomy i sarkomy Kaposhi (klinicheskiy sluchay) [in Russian]. Dermatovenereologiya. *Kosmetologiya*. 2022; 8(1):75-83. https://doi.org/10.34883/PI.2022.8.1.012
14. Altunay I., Kucukunal A., Demirei G.T., Ates B. Variable clinical presentations of Classic Kaposi Sarcoma in Turkish patients. J. Dermatol. *Case Rep*. 2012; 6(1):8-13. https://doi.org/10.3315/jdcr.2012.1088
15. Hengge U.R., Ruzicka T., Tyring S.K. et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: Epidemiology, environmental predispositions, clinical manifestations, and therapy. *Lancet Infect. Dis*. 2002; 2(5):281-292. https://doi.org/10.1016/S1473-3099(02)00263-3
16. Bernardini B., Faggion D., Calabro L. et al. Imiquimod for the treatment of classical Kaposi's sarcoma. Acta Derm. *Venereol*. 2010; 90(4):417-418. https://doi.org/10.2340/00015555-0850
17. Prokofiev A.A., Molochkov V.A., Molochkov A.V. et al. Photodynamic therapy for Kaposi's sarcoma (Fotodinamicheskaya terapiya sarkomy Kaposhi) [in Russian]. *Ros. zhurnal kozhn. i ven. bolezney*. 2011; 4:(4-6).
18. Kartashova M.G., Malinovskaya V.V. Immunocorrective therapy of patients with Kaposi's sarcoma with Viferon (Immunokorrigiruyushchaya terapiya bol'nykh sarkomoy Kaposhi preparatom Viferon) [in Russian]. *Immunologiya*. 2008; 4:227-229.
19. Kazantseva K.V., Molochkov A.V., Molochkov V.A. et al. Kaposi's sarcoma: pathogenesis, clinic, diagnosis and modern methods of treatment (Sarkoma Kaposhi: patogenez, klinika, diagnostika i sovremennyye metody lecheniya) [in Russian]. *Ros. zhurnal kozhn. i ven. Bolezney*. 2015; 1:7-14.