Iatrogenic Kaposi's sarcoma following therapy for rheumatoid arthritis

Beata Bergler-Czop[1], Ligia Brzezińska-Wcisło[1], Magdalena Kolanko[2]

[1]Chair and Department of Dermatology, School of Medicine, Medical University of Silesia, Katowice, Poland
[2]Department of Dermatology, Mielecki's Public Hospital, Katowice, Poland

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Kaposi's sarcoma is an angioproliferative disorder, with four subtypes: iatrogenic, acquired immune deficiency syndrome (AIDS) related, African, and classic. The disease has a viral etiology and a multifactorial pathogenesis hinged on an immune dysfunction. Changes are multifocal, with a course ranging from indolent, with only skin manifestations, to fulminant, with extensive visceral involvement [1, 2]. An increased incidence of Kaposi's sarcoma has been described in organ transplant recipients receiving immunosuppressive therapy. In addition, Kaposi's sarcoma has been reported in patients treated with corticosteroid therapy. In the current view, all forms of Kaposi's sarcoma have a common etiology in human herpesvirus (HHV)-8 infection, and the differences among them are due to the involvement of various cofactors. In fact, HHV-8 infection can be considered a necessary but not sufficient condition for the development of the disease, because further factors (genetic, immunologic, and environmental) are required. The role of cofactors can be attributed to their ability to interact with HHV-8, to affect the immune system, or to act as vasoactive agents. In this contribution, a survey of the current state of knowledge on many and various factors involved in Kaposi's sarcoma pathogenesis is carried out, in particular by highlighting the facts and controversies about the role of some drugs (quinine analogs and angiotensin-converting enzyme inhibitors) in the onset of the disease [3–6]. It is possible that the same agents may act as either stimulating or inhibiting cofactors according to the patient's genetic background and variable interactions. Treatment guidelines for each form of Kaposi's sarcoma are outlined, because a unique standard therapy for all of them cannot be considered due to heterogeneity of the disease. Management, which may depend on a variety of factors including the clinicopathologic type of Kaposi's sarcoma and results of staging, ranges from no treatment to local measures such as intralesional vinblastine or systemic administration of cytotoxic chemotherapy for disseminated disease [1, 7–10].

We present an interesting case of iatrogenic Kaposi's sarcoma, in which we considered three cofactors: immunosuppression, corticosteroids and anti-TNF-α antibody.

The 57-year-old Caucasian woman was admitted to the Dermatology Department in 2014 because of extensive, multiple purple and brown plaques and nodules on all four extremities (Figure 1). She had a 5-year history of rheumatoid arthritis, treated in the Rheumatology Department, initially with sulfasalazine and methylprednisolone. Because of insufficient effects, therapy was continued with corticosteroids and methotrexate (orally and subcutaneous), and after that, due to methotrexate side effects, with corticosteroids and cyclosporine A. Skin lesions appeared as small purple patches in lower extremities in 2012 and were slowly spreading. The rheumatoid arthritis still had an aggressive course, and the rheumatologist began therapy with certolizumab (anti-TNF-α) in June 2013. During this treatment the skin lesions dramatically enlarged and spread to the upper extremities. Rheumatoid vasculitis was diagnosed and rheumatologists started treatment with methylprednisolone (max. 48 mg/day) and cyclophosphamide intravenous pulses – skin lesions were still systematically increasing. When the patient was admitted to our department in January 2014, she took corticosteroids – methylprednisolone (16 mg/day) and azathioprine (100 mg/day) therapy. Chest X-ray, abdominal ultrasonography and lower extremity Doppler, chest and abdomen computed tomography (CT) did not detect any visceral lesions. Biopsy specimens obtained from the lesions on the lower extremities confirmed the diagnosis of Kaposi's sarcoma (Figure 2). The test for HIV was negative. The diagnosis of iatrogenic Kaposi's sarcoma was established. The treatment with azathioprine

Address for correspondence: Beata Bergler-Czop, 2a Leśna St, 42-624 Ossy, Poland, phone/fax: +48 32 284 08 77, e-mail: bettina2@tlen.pl
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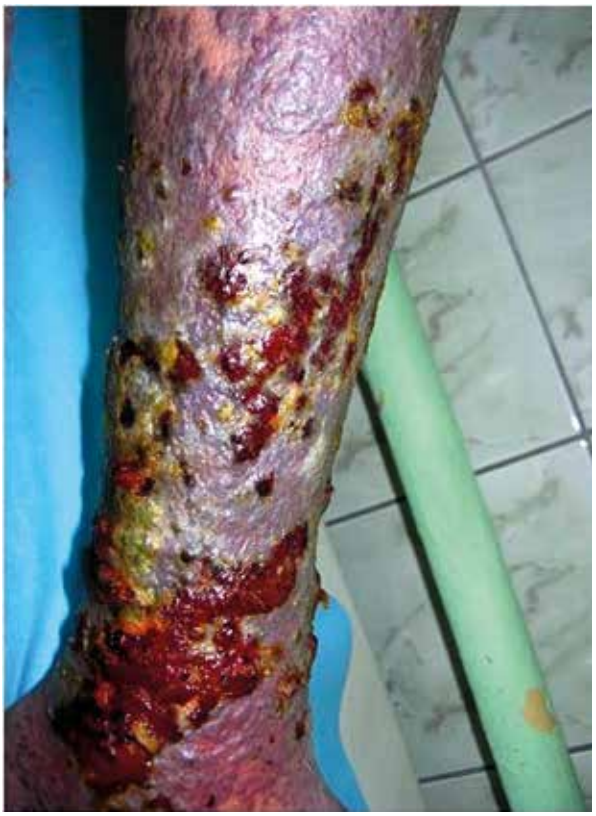

Figure 1. Multiple, dark-red colored nodules on the extremities that were several centimeters in size

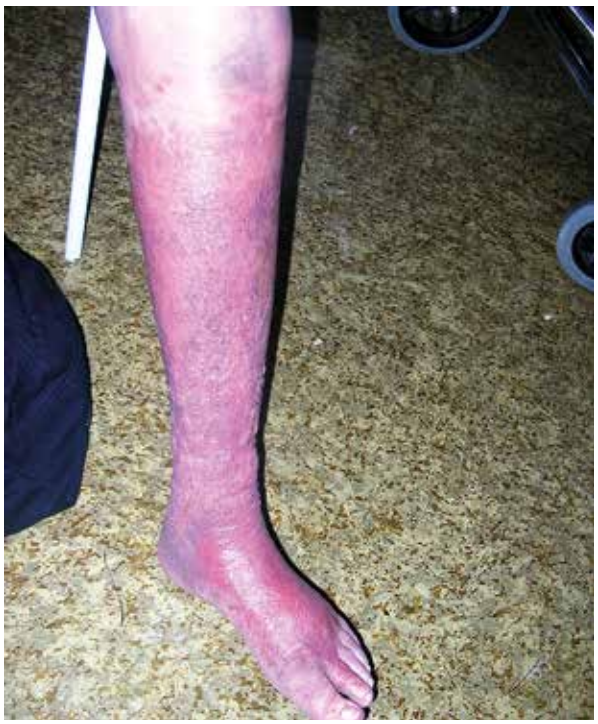

Figure 3. After the treatment and cessation of corticosteroids, immunosuppression and anti-TNF-α therapy the skin nodules decreased in size and number

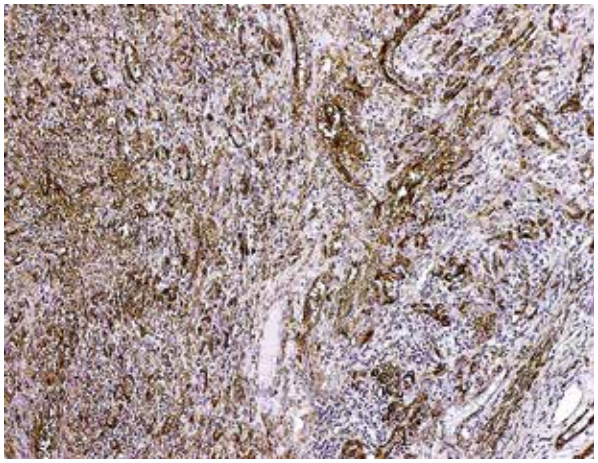

Figure 2. Histological picture (immunohistochemical reaction (SMA) with DAB), CD 31+, CD 34+, Bcl+

was discontinued and treatment in the Oncology Department was started doxorubicin and dacarbazine. Now the stable disease (RECIST Guidelines) is observed. The patient is currently under the supervision of Dermatology, Oncology and Rheumatology Clinics (Figure 3).

Kaposi's sarcoma is a low-grade angioproliferative tumor associated with Kaposi's sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV-8) infection. Its multifactorial pathogenesis hinges on an immune dysfunction [1, 2, 11].

Newer histologic variants include anaplastic, hyperkeratotic, lymphangioma-like, bullous, telangiectatic, ecchymotic, keloidal, pyogenic granuloma-like, micronodular, intravascular, glomeruloid and pigmented, as well as Kaposi's sarcoma with sarcoid-like granulomas and with myoid nodules. Latency-associated nuclear antigen (HHV-8) is the most specific

immunohistochemical marker available to help distinguish Kaposi's sarcoma from its mimics [2, 12]. The disease is multifocal, with a course ranging from indolent, with only skin manifestations, to fulminant, with extensive visceral involvement [1, 13, 14]. In our case only the skin was involved.

An increased incidence of Kaposi's sarcoma has been described in organ transplant recipients receiving immunosuppressive therapy. In these cases it usually occurs later than one year after the drugs were first administered. In addition, Kaposi's sarcoma has been reported in patients treated with corticosteroid therapy. In our patient we considered three possible cofactors: immunosuppression, corticosteroids and anti-TNF-α antibody (certolizumab).

Based on these assessments, it is possible to hypothesize that the role of cofactors in this disease pathogenesis can move toward an effect either favoring or inhibiting the onset of the disease, depending on the presence of other agents modulating the pathogenesis itself, such as genetic predisposition, environmental factors or

lymph flow disorders. It is possible that the same agents may act as either stimulating or inhibiting cofactors according to the patient's genetic background and variable interactions [15].

Iatrogenic Kaposi's sarcoma was first described among organ transplant recipients. It has been reported less frequently during immunosuppressive therapy for a variety of clinical disorders such as rheumatologic disease, hematologic disease and pulmonary disease. More recently, corticosteroid therapy has been associated with the development [1, 4].

The mechanism of corticosteroid action involves passive diffusion through the cell membrane, movement to the nucleus and regulation of the transcription of target genes. Systemic corticosteroids are potent immunosuppressive and anti-inflammatory agents. Recently, it was demonstrated that there is strong inhibition of apoptosis by glucocorticoids at the transcriptional level at all stages of fibrosarcoma development. The regulation of tumor cell death by corticosteroids was shown *in vitro* during tumorigenesis [1, 3, 14].

The prognosis of corticosteroid-induced Kaposi's sarcoma is unpredictable. In about half of the cases, cessation of the corticosteroid is followed by resolution of the sarcoma, whereas in the other half, it progresses. These variable outcomes suggest that steroids are responsible for induction of precipitating factors for Kaposi's sarcoma [3]. In our patient we observed stabilization and improvement of the dermatological stage. Now our patient is under the supervision of Dermatology Oncology and Rheumatology Clinics. In the Rheumatology Department treatment is being established, and it is a problem, because of the contraindication for immunosuppression and corticosteroids.

Conflict of interest

The authors declare no conflict of interest.

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