SHORT COMMUNICATIONS

HIV/AIDS-ASSOCIATED KAPOSI’S SARCOMA WITH MULTIPLE SKIN-MUCOSAL DISSEMINATIONS FOLLOWING ULTRAVIOLET (PUVA) PHOTOCHEMOTHERAPY

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ABSTRACT
HIV/AIDS infection in Bulgaria has spread over about 1200 registered patients and it is supposed that the number of the undetected cases is four times higher. Kaposi’s sarcoma is rarely observed in our country and no cutaneous-mucosal dissemination is reported for the time being.

AIM: The aim of the study is to present a case of disseminated Kaposi’s sarcoma in a HIV/AIDS patient who underwent Psoralen - UVA radiation treatment (PUVA) for total alopecia.

METHODS: HIV was proved through ELISA and Western blot (InnoLia HIV I/II Score). PCR method (COBAS-Amplicor HIV-1 MT, 1,5) was used to determine viral load (VL). Monitoring was realized by flow-cytometric phenotype analysis of the immune cells. Biopsy of a skin lesion was performed for histomorphological analysis. Computed axial tomography (CAT) of the visceral organs was also applied.

RESULTS: The patient’s face, chest, back and upper extremities are covered by more than 50 typical for Kaposi’s sarcoma skin tumors and several isolated lesions are found in the oral cavity mucosa. The histological results show dilated vascular spaces with large endothelial cells and spindle-like tumor cells in irregularly formed fascicles. Monitoring of the immune cells and the viral load before and after the application of highly active antiretroviral therapy (HAART) showed CD4+ T cell number = 0.147x10⁹/l and VL = 216 000 copies HIV-RNA/ml plasma when the disorder was first detected. A very good effect appeared 4 months after the HAART start: the mucous membrane lesions disappeared and the skin tumors decreased by number and dimensions. In the same time the CD4+ T cell number increased up to 0.255x10⁹/l and VL values decreased < 400 c/ml.

CONCLUSION: Disseminated form of Kaposi’s sarcoma can be provoked by additional immunosuppressive factors like the implementation of PUVA therapy. Early initiation of HAART improves the process and prevents visceral dissemination.

Key words: Kaposi’s sarcoma, skin-mucosal dissemination, HIV/AIDS, PUVA-photo-chemotherapy, HAART

INTRODUCTION
Kaposi’s sarcoma (KS) is the first reported malignant tumor associated with HIV-infection. Till 1980 when it first appeared in HIV/AIDS-patients it was a very rare type of sarcoma and affected mainly elderly men in Eastern Europe and the Mediterranean region. Nowadays Kaposi’s sarcoma is most often found in HIV/AIDS and it can affect about 20% of the untreated patients. When internal organs are additionally involved the disease may lead to a fatal end. The aim of this study was to present a case of rapid and aggressive cutaneous-mucosal dissemination of KS in a HIV/AIDS patient who underwent Psoralen-ultraviolet radiation therapy (PUVA) for total alopecia, as well as the effect of highly active antiretroviral therapy (HAART) in such cases.

METHODS
HIV infection was proved at the National confirming laboratory on HIV/AIDS through ELISA and Western blot (InnoLia HIV I/II Score). The immune cells (CD3+,CD4+,CD8+,CD19+,CD56+) were...
phenotype analyzed (Flow-cytometry) with determination of the absolute number and percentage of the leukocyte subpopulations. The viral load (VL), expressed by the number of HIV-RNA copies in a ml of plasma (HIV-RNA copies/ml) was determined by a quantitative PCR test (ROCHE; COBAS-Amplicor HIV-1 Monitor Test, version 1.5). Skin lesion biopsy material was examined histologically. Routine clinical-laboratory and microbiological investigation as well as scanning of the visceral organs were also performed.

RESULTS

The patient we present is a 30 years male who was HIV infected in a heterosexual way. He supposes it happened in 2000 when he divorced and indulged in promiscuous sex with different women including country and foreigner sex-workers. At the end of 2006 the patient got total hair fall out. After a two-year unsuccessful treatment with local medical agents the patient underwent over 20 intensive sessions with Psoralen-ultraviolet radiation (PUVA). The physician who applied PUVA-course was not aware of the patient’s HIV status. In the course of radiation therapy the patient noticed a small rounded bluish formation under his eye. At the end of the sessions and immediately after them numerous similar new formations appeared on the skin of the body and upper extremities most of them increasing in dimensions. Tumor infiltrates appeared in the oral cavity mucosa as well. The patient pulled through bronchopneumonia. He turned to the Clinic of Infectious Diseases where we observed multiple erythematosus to bluish-violaceous, painless, non-bleeding plaques and nodules on the skin as well as several isolated lesions on the oropharyngeal mucous membrane. The disorder was diagnosed as Kaposi’s sarcoma. Biopsy of a lesion was performed. No clinical and CAT data of visceral involvement were found. So we initiated HAART. The photographs demonstrate diffuse skin damage of the head, body and the upper extremities with more than 50 tumor formations (Fig. 1, 2, 3). Histological data show dilated vascular spaces with large endothelial cells, extravasating erythrocytes and dermal hemosiderin deposits. Spindle-like cells in irregularly formed fascicles were also found (Fig. 4). Table 1 presents the results of immune cells and viral load monitoring before and after HAART application.

Figure 1 and Figure 2. Multiple Kaposi’s sarcoma tumor formations on the skin of body and extremities.
Kaposi’s sarcoma is a vascular tumor which affects the skin, mucous membranes, lymph nodes and the internal organs. It presents proliferation of the endothelial cells which is induced by the human herpes-virus 8 (HHV-8) and is manifested with four epidemiologic forms. More than a century ago the Hungarian dermatologist Moritz Kaposi described the first form of Kaposi’s sarcoma which was called Classic KS. It affected elderly men from the Mediterranean region and Eastern Europe and caused deforming and often painful but not fatal tumors of the lower extremities. The second form – African endemic KS is more aggressive and rapidly disseminates into the tissues under the skin, the bone and lymphatic systems as well as into the visceral organs. This fatal form of Kaposi’s sarcoma affects mainly children and young adults from sub-Saharan Africa. The third, iatrogenic form is also aggressive and it is reported to be found in organ-transplanted patients on immunosuppressive therapy. The fourth form, HIV-induced KS, is one of the first sufferings observed in HIV-infected patients and it is an AIDS-defining disease. In contrast to the classic KS form, the tumor formations in HIV-induced KS affect the upper part of the body and they may also appear on the mucous membranes. It is one of the most aggressive KS forms whose lesions can be found in the stomach, intestines, lymph nodes and the lungs. Independent of the clinical-epidemiological variant HHV-8-DNA was present in almost all KS lesions. Nevertheless it is well known that HHV-8 is a necessary
but not independent causative factor for KS. It is quite probable that HHV-8 acts in combination with some proinflammatory and angiogenic factors, such as altered patient’s response to some cytokines and to HIV-1 trans-activator protein Tat which promotes endothelial cell growth. The genes encoded by HHV-8’s DNA have the potential to provoke cell proliferation and prevent apoptosis.\textsuperscript{3,4} Furthermore, the latency-associated-nuclear-antigen-type-1 protein (LANA-1 protein) is strongly expressed in the characteristic for KS spindle-like cells which is considered to be important for sustaining certain malignancy associated with the Kaposi’s sarcoma-Herpes virus (KS-HV).\textsuperscript{1,4,5} Clinically KS in the early stage is manifested by pink patches that turn into reddish or brownish papules and plaques often evolving into nodular forms. It is quite common to involve mucous membrane surfaces in the process.\textsuperscript{2} Visceral dissemination of the tumors is characteristic for the aggressive forms. The histological characteristics of KS are identical for the four clinical forms and they include: neoangiogenesis, inflammation and cellular proliferation.\textsuperscript{5} The inflammatory infiltrate is prominent above the skin and typically precedes spindle tumor cells formation. Spindle-like cells are disorganized and dispersed among the stromal cells. Eosinophilic hyaline globules which are thought to represent remnants of erythrocytes phagocytosed by the tumor cells, are present within the cytoplasm of the spindle cells or extracellularly.\textsuperscript{4,9} The lesions themselves are vascularised and contain slit-like vascular channels surrounding a pre-existing blood vessel. No atypia and mitotic activity are found in the endothelial cell monolayer. Extravasating erythrocytes and hemosiderin deposits can be seen in the dermis.\textsuperscript{2} The KS-lesions may shrink upon

### Table 1. Monitoring of immune cells and viral load in a patient with Kaposi’s sarcoma

<table>
<thead>
<tr>
<th>Leukocyte subpopulation</th>
<th>Absolute number of the leukocyte subpopulation (Cell number x10^9/l)</th>
<th>Reference Limits*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Flowcytometric detection of the leukocyte subpopulation</td>
<td>At patient’s presentation in the clinic</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.314</td>
<td>1.131</td>
</tr>
<tr>
<td>Total T-cells CD3+</td>
<td>1.064</td>
<td>0.809</td>
</tr>
<tr>
<td>T-helper-inducer CD3+CD4+</td>
<td>0.147</td>
<td>0.255</td>
</tr>
<tr>
<td>T-suppressor/cytotoxic CD3+CD8+</td>
<td>0.874</td>
<td>0.520</td>
</tr>
<tr>
<td>Total B cells CD19+</td>
<td>0.132</td>
<td>0.161</td>
</tr>
<tr>
<td>NK cells CD3-CD56+</td>
<td>0.111</td>
<td>0.159</td>
</tr>
</tbody>
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<th>Percentage of the leukocyte subpopulation</th>
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<tbody>
<tr>
<td>Total T-cells CD3+</td>
</tr>
<tr>
<td>T-helper-inducer CD3+CD4+</td>
</tr>
<tr>
<td>T-suppressor/cytotoxic CD3+CD8+</td>
</tr>
<tr>
<td>Total B cells CD19+</td>
</tr>
<tr>
<td>NK cells CD3-CD56+</td>
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<tr>
<td>CD4/CD8 index</td>
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<tr>
<th>Viral load (VL)</th>
<th>HIV-RNA copies/ml</th>
<th>Limit of distinguishable VL copies/ml**</th>
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<tr>
<td>Automatic quantitative PCR test</td>
<td>VL = 216 000</td>
<td>VL &lt; 400</td>
</tr>
</tbody>
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* Laboratory test complex at the National centre of infectious and parasitic diseases (NCIPD). Authorized laboratory of immunology and allergology, Sofia.

** NCIPD, National confirming laboratory of HIV/AIDS, Sofia.
first starting HAART.5-7 Such a phenomenon was observed in our patient, whose treatment included a combination of three reverse transcriptase inhibitors - two nucleoside analogs (abacavir, lamivudin) and one non-nucleoside (efavirenz). After four months of treatment the effect was: disappearing of the formations in the oral cavity, skin lesions regress and fading, an increase of CD4+ cells number and decrease of VL values. Six months after HAART initiation the number of CD4+ T cells kept above the critical threshold for opportunistic infections and their percentage increased more than two times, the CD4/CD8 index was significantly increased and the viral load was below distinguishable values (Tabl. 1). Various effects of HAART in KS-patients are described in literature and different combinations of medicines are recommend but the common standpoint of all authors is on the immediate start and the favourable effect of applying such a therapy.5,6,7 We did not find out initial or additional manifestations of any KS visceral dissemination. In contrast to the African type, rarely and predominantly isolated KS skin lesions in HIV/AIDS patients have been observed in Bulgaria. Why such a dissemination appeared in a patient whose CD4+ lymphocytes (although strongly decreased before HAART treatment) had not reached the critical values of isolated T-cells in a microliter of plasma, as we observed in a number of HIV/AIDS patients without KS manifestation, is difficult to explain.8,10 The role of some medical lotions used by the patient for alopecia treatment and especially PUVA may be suspected to be provoking factors for dissemination. Psoralen toxic effects are well known and documented, and laboratory data show activation of the HIV-1 genome at exposure to UV-radiation, including PUVA. It is reported that UV-radiation may help cancerogenesis through either direct induction of DNA-damages or through reduction of the immune system effectiveness in its role to keep certain herpes viruses under control.11 Breuer-McHam et al. found that ultraviolet radiation induced HIV activation in the skin and they supposed the mechanism was associated with Tat and G2M arrest. The authors also supposed that HIV activation might be inhibited by NF-kB blocking agents.12,13 We could find out only one literature report on a KS’s rapid and aggressive onset in a patient with psoriasis, where the authors discussed the preliminarily applied methods of psoriasis medical treatment.14

**CONCLUSIONS**

Besides HIV-induced immune insufficiency and promiscuity which facilitated meeting and infecting with HHV-8, Kaposi’s sarcoma and especially the rapid disseminated form of the tumor in our patient may be associated with the co-participation of some additional toxic and immunosuppressive factors such as PUVA-photochemotherapy. There are indications that in patients whose blood VL is reduced to undetectable values thanks to HAART, the process of KS dissemination can be stabilized or reversed and in that way involvement of visceral organs can be avoided. For the present the clinical case described by us arouses hopes on a favourite outcome of the process.

**REFERENCES**


HIV/AIDS-Associated Kaposi’s Sarcoma with Multiple Skin-mucosal Disseminations Following Ultraviolet (PUVA) Photochemotherapy

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**Chronology**

Kaposi’s sarcoma is a disease that affects the skin and mucous membranes, often characterized by purple patches or nodules. It is associated with HIV/AIDS, especially in patients with a low CD4+ T cell count. The disease can spread to internal organs, leading to advanced stages of the disease and increased mortality. Photochemotherapy with Ultraviolet A (PUVA) has been used as a treatment option, but its effectiveness varies among patients. The study described the case of a patient with advanced HIV/AIDS, who developed widespread skin and mucosal lesions after PUVA therapy. The patient’s CD4+ T cell count was low, and there was a significant increase in the viral load. Despite treatment, the disease progressed, and the patient eventually succumbed to the complications of HIV/AIDS.

The study highlights the challenges in treating HIV/AIDS patients and the need for improved therapeutic strategies. It also underscores the importance of early detection and aggressive treatment to prevent the spread of Kaposi’s sarcoma.

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**RÉSUMÉ**

Kaposi’s sarcoma con acompaña con diseminación cutánea múltiple y mucosa en caso de infección por el virus de la inmunodeficiencia humana (VIH). La terapia fotofotocimioterapia con ultravioleta (PUVA) se ha utilizado como tratamiento para este tipo de enfermedad. Los pacientes con VIH/AIDS pueden desarrollar casos agudos e inesperados de Kaposi’s sarcoma, lo cual se ha descrito en casos de psoriasis. Se presenta el caso de un paciente con VIH/AIDS que desarrolló diseminación cutánea múltiple y mucosa después de tratamiento con PUVA. El paciente presentó un número bajísimo de células CD4+ y elevada carga viral antes del tratamiento, lo cual se mantuvo constante durante el tratamiento. A pesar de la terapia fotofotocimioterapia con ultravioleta (PUVA), la enfermedad avanzó, lo que llevó a la muerte del paciente.

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**Заключение:** Диссеминированные формы Kaposi’s sarcoma могут быть спровоцированы дополнительными иммуносупрессирующими факторами, как PUVA терапия. Раннее стартирование HAART улучшает процесс и предотвращает висцеральную диссеминацию.