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Classic Kaposi's Sarcoma: A Case Report

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SUMMARY A 60-year-old male from the Mediterranean area presented with edematous right leg and livid nodules and macules on the skin of upper and lower extremities. Biopsy specimen obtained from the right upper leg showed a pathohistologic finding indicative of Kaposi's sarcoma. Polymerase chain reaction testing revealed HHV-8 in the skin lesion. Serology for HIV was negative. Additional examinations did not reveal dissemination of the disease. Negative HIV serology, normal laboratory findings and absence of immunosuppressant therapy in the patient's history confirmed the diagnosis of the classic form of Kaposi's sarcoma.

KEY WORDS: classic Kaposi's sarcoma; HHV-8 infection

INTRODUCTION

Kaposi's sarcoma (KS) was first described in 1872 by the Hungarian dermatologist Moritz Kaposi. He named it "idiopathic, multiple, pigmented sarcoma". Although it was more than a century ago its biology remains as enigmatic and conflicting. In the early 1980s, the prevalence of KS began to increase dramatically and it soon became the most common malignancy among patients with the acquired immunodeficiency syndrome (AIDS), especially male homosexuals. However, its etiology and pathogenesis have not been elucidated so far. In 1994, Chang *et al*. reported on a finding of human herpesvirus 8 (HHV-8) DNA sequences in tumor lesions and peripheral blood mononuclear cells from patients with KS (1). This shed more light on the possible etiopathogenetic mechanisms of the disease. Four types of KS have been recognized: classic, endemic (African), iatrogenic, and epidemic (AIDS related).

We report on a case of classic KS in a 60-year-old man, manifested with edematous right leg, and livid nodules and macules on the skin of the upper and lower extremities.

CASE REPORT

A 60-year-old male was admitted to University Department of Medicine, Merkur University Hospital in Zagreb for the occurrence of livid nodules and macules on the skin of the upper and lower extremities. The patient came from a town on the Adriatic Sea in the Mediterranean area. Twenty years before, he had spilled caustic soda on his right leg and since then he observed occasional swelling of the leg. He was admitted to the hospital in his town because of bilateral pneumonia at the beginning of March 2003. During that period, first skin lesions occurred. His legs were edematous.

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Several months later his right leg was still swollen. Phlebography of the right leg suggested partial recanalization after phlebothrombosis in the proximal upper leg. Extirpation of the great saphenous vein was performed, along with biopsy of the skin lesions. Pathologic finding suggested KS and he was referred to our hospital for further evaluation. There was a possibility of positive family history of the disease, as the patient's father had some black spots on his legs. Physical examination revealed numerous nodes and macules of 0.5-2 cm in diameter, distributed mostly over the edematous lower right extremity (Fig. 1).

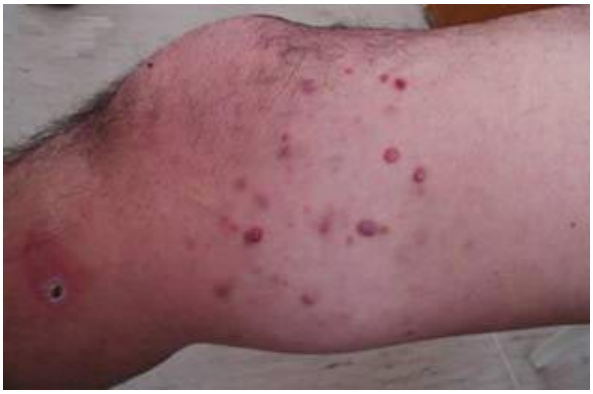

Figure 1. Multiple nodules on right lower limb.

Laboratory findings, i.e.complete blood count, urinalysis, renal and hepatic function tests, were within the normal limits. Lung x-ray revealed post-tuberculosis changes in the lymph nodes of the right hilus, without any infiltrative changes or effusion. Serology for human immunodeficiency virus (HIV) was negative. T lymphocyte count was normal, whereas CD4+ and CD8 cell count was slightly reduced and marginally elevated, respectively. There was also a reduction in B lymphocyte count and an increase in NK-cell count. Ultrasound of the abdomen and heart was normal. Doppler sonography of the edematous lower extremity deep veins was normal, and so was ultrasound of the groin. Colonoscopy and endoscopic examination of the upper gastrointestinal tract revealed no pathologic changes suggestive of KS.

PCR testing detected HHV-8 in skin lesion

DNA was isolated from a 10-µm section of formalin-fixed and paraffin-embedded biopsy of a KS lesion, as described elsewhere (2). The section was deparaffinized with Histoclear II (National Diagnostics, Hessle Hull, England), washed with 100% ethanol, resuspended in digestion buffer (50 mM Tris-HCl pH 8.5, 1 mM EDTA, 0.5% Tween 20) and digested with proteinase K (Roche Diagnostics, Mannheim, Germany) at final concentration of 200 µg/mL overnight at 37° C. The sample was boiled for 8 min before proceeding to PCR.

PCR analysis for HHV-8 sequence

Samples were submitted to 35 amplification cycels (94° C for 1 minute, 54° C for 1 minute, 72 °C for 1 minute) according to Daibata *et al*. (3). HHV-8 DNA was amplified with the primers 5'-AGCCGAAAGGATTCCACCAT-3' and 5'-TCCGTGTTGTCTACGTCCAG-3', resulting in generation of a 233-bp fragment. The PCR products were submitted to electrophoresis on a 3% ethidium bromide-stained agarose gel allowing for direct visualization of bands of an appropriate size. All procedures were performed under strict conditions to avoid false-positive results. As a positive amplification control, MSH2 gene (NCBI NM000251) was detected in both samples prior to HHV-8 assay. HHV-8 sequence was detected in the biopsy specimen of the KS lesion, whereas the patient's peripheral blood was negative for HHV-8 (Fig.2).

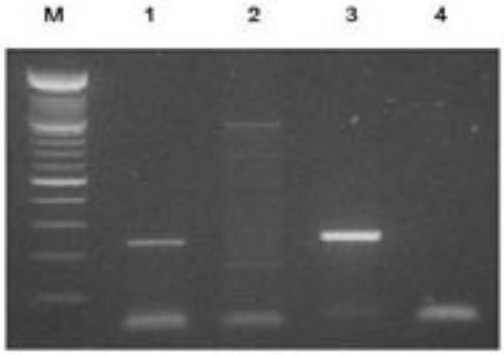

Figure 2. HHV-8 detection. Ethidium-bromide stained gel. M: molecular weight marker VIX (Roche Diagnostics, Mannheim, Germany), lane 1: positive control, lane 2: peripheral blood of the patient, lane 3: Kaposi's sarcoma lesion, lane 4: negative control (water).

Histologically, in a segment of the skin and subcutis, a lobular tumor, built of vascular spaces and bordered by elongated and uniform cells, was found. There were also some mastocytes and rare lymphocytes. CD 105 and CD 31 were positive in tumor cells. The pathological finding correlates with Kaposi's sarcoma (Fig. 3).

In our opinion, negative HIV serology, normal laboratory findings, and absence of immunosuppressant therapy in the patient's history strongly indicated the diagnosis of the classic form of the disease. In accordance with previous literature

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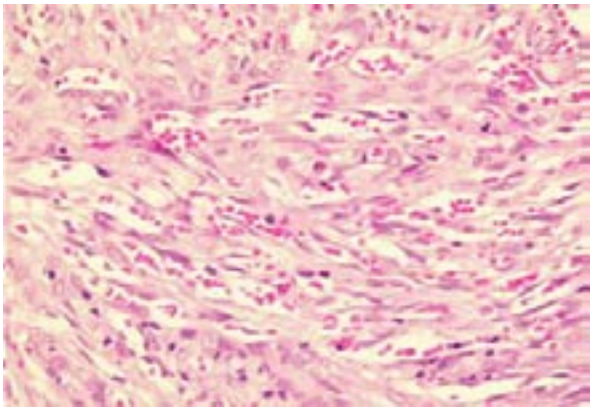

Figure 3. Proliferation on small vessels bordered by elongated and uniform cells. (Hematoxylin - eosin stain; x250)

reports, these results confirmed the possible etiopathogenetic role of HHV-8 in classic KS.

DISCUSSION

KS is a spindle-cell tumor thought to derive from endothelial cell lineage (4). Typical histologic findings include proliferation of spindle cells, prominent slit-like vascular spaces, and extravasated red blood cells (5). There is often a significant component of inflammatory infiltrate including lymphocytes and macrophages. This condition carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement. KS causes red or purple patches (lesions) on the skin and/or mucous membranes. Lesions may also develop in the oral cavity, gastrointestinal tract, lymph nodes, liver, lungs, kidneys, and spleen (6-8). The disease is clinically significant due to its possible multicentric involvement of the internal organs being a cause of death in most cases.

Based on the clinical and epidemiologic features, four types of KS have been recognized.

- *Classic KS* is most commonly seen in Israel among elderly male Jews, Italians and Greeks but also in people of the Mediterranean, East European and North American ancestry (9-11). The highest incidence rates of classic KS in Europe have been recorded in Sicily (Ragusa, 30.1 per million in men, 5.4 per million in women) and Sardinia (24.3 per million in men, 7.7 per million in women) (10). Histologic features of classic KS are not different from other forms of the disease (9,12). It usually occurs between the fifth and sixth decade of life, in Africans even earlier, in the third or fourth decade, more frequently in males. Data on male to female ratio are different, several reports state a 10:1 male to female ratio, and others a significantly lower figure of 3:1 (4,9). Classic KS usually carries a protracted and indolent course. On rare occasions the disease can have aggressive behavior with disseminated skin lesions and involvement of internal organs (13). Common complications include venous stasis and lymphedema. As many as 30% of patients with classic KS may subsequently develop a second malignancy. Visceral involvement is uncommon. The treatment of classic KS depends on the site of lesions and clinical signs of the disease. Observation may be appropriate for asymptomatic individuals with little progression over a long period. Patients with lesions in limited areas are often treated with radiation therapy (14,15).

- *Endemic African KS* occurs in HIV seronegative men in Africa and may carry an indolent or aggressive course.

- *Iatrogenic (immunocompromised) KS* occurs after solid-organ transplantation or in patients receiving immunosuppressive therapy. However, individuals with congenital immunodeficient states are not at an increased risk of developing KS. The average time of KS following transplantation to develop is 30 months. Visceral involvement is common.

- *Epidemic AIDS-related KS* occurs in patients with advanced HIV infection, and is the most common presentation of KS. In the United States, KS serves as an AIDS-defining illness in 10%-15% of HIV-infected homosexual men. In Africa and developing regions, epidemic AIDS-related KS is common in heterosexual adults and occurs less often in children. Visceral involvement is common. AIDS-related KS is the most clinically aggressive form of KS (16).

HHV-8 is a gamma herpesvirus, closely related to Epstein-Barr virus and *Herpesvirus saimiri* (1,17). Gamma herpesviruses are lymphotropic viruses that play a role in cell proliferation and malignancies. Several other diseases are associated with HHV-8 infection such as body cavity-based lymphomas, Castleman disease and leiomyosarcomas that occur in HIV positive individuals (18). Later studies confirmed HHV-8 DNA sequences from lesions of classic, endemic, iatrogenic and HIV-associated forms of KS (19-25). The universal detection of HHV-8 suggests its central role in the development of KS. In contrast, careful PCR testing does not detect HHV-8 in the normal tissues.

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As with other cell-transforming human DNA viruses, infection with HHV-8 alone is not sufficient for the development of tumor and additional factors such as immunosuppression are required (19,26). Some other studies show that HHV-8 certainly has the means to overcome cellular control and immune responses and thus to predispose carriers to malignancy, particularly KS (27). However, the interplay between infection with HHV-8 and other factors is complicated and our understanding of the induction and development of the disease is still incomplete.

In situ PCR and immunohistochemistry demonstrate that HHV-8 is primarily localized to the spindle and endothelial cells (28-31). It is currently debated whether the KS tumor represents a reactive process or it is a true monoclonal proliferation of a transformed cell (32-34). Human herpesvirus 8 DNA can be amplified from KS tissue in different clinical stages of the disease (35). Furthermore, semiquantitative analysis has established that the HHV-8 DNA load is higher in patients with multicentric and visceral involvement compared with those with localized disease, and that the nodular stage has also a higher viral load than do the patch and plaque stages, thereby showing a correlation between viral load and disease severity (36). Although the virus is tropic for lymphocytes, peripheral blood mononuclear cells (PBMCs) are only sporadically positive on PCR testing. Even in patients with KS, PBMCs are positive in only about 50 percent (37). In addition, antibodies to HHV-8 are associated with KS or being at increased risk of developing KS. In other words, serologic testing demonstrates that infection with HHV-8 precedes and is predictive of the development of KS (38,39).

HHV-8 is principally acquired sexually. Anal intercourse may be particularly associated with transmission (40). HHV-8 is present in prostate tissue, semen, feces and saliva. Data concerning a vertical route of transmission of HHV-8 are contradictory (27). Intrafamilial person-to-person spread of the virus has also been suggested, since the HHV-8 seroprevalence of spouses, children, and siblings in families of KS patients is higher than in HHV-8 non-family controls (27). It can also be transmitted *via* solid organ transplantation (41).
Most serologic studies suggest a global HHV-8 seroprevalence of 2% to 10% (42). There is a significant geographic variation in the seroprevalence of the virus. In North America and in northern Europe 30%-50% of HIV positive homosexual men are seropositive for HHV-8, whereas among HIV negative homosexuals 15%-20% are HHV-8 positive. On the other hand, the infection appears to be uncommon in the general population. Current seroepidemiologic studies have suggested a high prevalence of HHV-8 in populations where classic KS is reported more frequently (the Mediterranean area), while there is a very high seroprevalence in many regions of Africa, and in China and Taiwan (approximately 50 percent) (41).

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