NON-AIDS KAPOSI’S SARCOMA IN THE HEAD AND NECK AREA

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Abstract: Kaposi’s sarcoma is classified into 4 types: classic (sporadic), African (endemic), iatrogenic (transplant recipients), and epidemic (acquired immunodeficiency syndrome [AIDS]-associated). This article aims to feature a comprehensive review of non-AIDS Kaposi’s sarcoma, including literature review and report of 3 cases. Case material was from our hospital’s archive. Literature review was conducted via electronic and manual medical database searches. Biological aspects, diagnostic difficulties, investigation protocols, and management modalities are discussed.

Key words: Kaposi’s sarcoma; non-AIDS; HHV-8; head and neck; transplant

Described in 1872 as idiopathic multiple pigmented sarcoma,1 Kaposi’s sarcoma is a rare angioproliferative disease. Four clinical types are recognized: classic (sporadic, mainly in elderly patients of European, Jewish, and Mediterranean descent), African (endemic, mainly in Sub-Saharan Africa), iatrogenic (immunosuppression-associated, principally renal transplant-associated), and epidemic (acquired immunodeficiency syndrome [AIDS]-associated). The last type is reported in western countries to be between 1000 and 77,000 times more common than the non–human immunodeficiency virus (HIV)-associated.2,3

Type I Kaposi’s sarcoma (classic) typically manifests as cutaneous lesions of the lower extremities and trunk with a slow, indolent course and a tendency to develop multifocally. Visceral involvement occasionally occurs,4–6 although it is more frequent in type II and of course type IV.7 Most frequent sites of involvement for visceral Kaposi’s sarcoma include the lymph nodes, gastrointestinal (GI) tract, and lungs.6 Type II Kaposi’s sarcoma (African) can be distinguished in the adult (cutaneous) variant and childhood (lymphadenopathic/visceral) variant.8,9 Type III Kaposi’s sarcoma is mainly transplant-associated, but has
been reported in the context of other immunosuppressive conditions/treatment.

In contrast to type IV Kaposi’s sarcoma, which usually presents as a disseminated, fulminant form, non-AIDS Kaposi’s sarcoma seldom affects mucous membranes, and head and neck mucosal involvement is even more rare.\textsuperscript{8,10–12} The international literature focuses heavily on type I Kaposi’s sarcoma and its well-celebrated association with HIV. In contrast, the other types of Kaposi’s sarcoma lesion are underrepresented, even more so for the head and neck cases. However, the growing number of successful organ transplantations internationally translates to an increase of non-AIDS Kaposi’s sarcoma cases. Moreover, recent elucidation of molecular mechanisms associated with the disease suggests that it might appear in clinical and pathological settings further to the ones traditionally described. The aforementioned facts were the incentives behind this clinical review article, which includes an extensive review of the literature as well as case presentation.

\section*{CASE REPORTS}

Two type I and 1 type III head and neck Kaposi’s sarcoma cases are presented here. The patients were all men, aged between 55 and 78 years and of Greek origin. The medical history of the patients with type I Kaposi’s sarcoma was unrelated to the lesions.

One of the type I cases featured oral Kaposi’s sarcoma as a sole manifestation (primary oral Kaposi’s sarcoma), unusual to the common multifocal presentation of this type. Furthermore, it
featured an infrequent localization (bilateral red nodules at submandibular duct orifices, approximately 1 cm diameter each), compared with the most usual oral Kaposi’s sarcoma presentations in the palate or gingivae (Figure 1).

The second type I case featured a large (>3 cm diameter) hard palate lesion extending to the alveolar process, covered by ulcerated epithelium (Figure 1). He had a history of synchronous cutaneous lesions (upper and lower extremities bilaterally, abdomen, back), some of which had been irradiated.

The patient with type III Kaposi’s sarcoma featured a hard palate lesion (3 cm × 2 cm) extending to the soft palate junction. This was an initial presentation (primary oral Kaposi’s sarcoma), 21 months following renal allograft transplantation and immunosuppressive treatment with cyclosporine and cortisone. He subsequently developed multiple metachronous cutaneous lesions of the lower extremities and abdomen.

All patients were HIV-1, HIV-2, hepatitis B virus (HBV) and hepatitis C virus (HCV) negative. CT imaging of the head and neck area showed the
degree of osteolytic destruction (Figure 2) and excluded neck lymphadenopathy. CT of the chest and abdomen was normal for all patients.

Incisional biopsy and fine-needle aspiration biopsy (FNA) were obtained from all lesions. With regard to histopathology, formalin-fixed, paraffin-embedded 4-μm tissue sections were immunohistochemically stained using an automated staining machine (Ventana Medical Systems). Hematoxylin–eosin staining revealed characteristic features of Kaposi’s sarcoma, namely an atypical spindle-cell component and incomplete slit-like vascular channels of variable size with extravasated red blood cells (Figure 3). Immunostaining with a standard avidin–biotin–peroxidase technique for CD34 and factor VIII-related antigen was strongly positive (Figure 4). HHV8 immunohistochemistry was performed with the LNA-1 antibody (clone 13B10; Novocastra). All cases showed nuclear staining of variable intensity. Both the stained spindle and endothelial cells showed speckled dot-like nuclear pattern. The percentage of positive cells varied from 50% to 80% (Figure 5).

For cytological analysis, the aspiration material was processed using the liquid-based cytology technique (Thinprep: automated processing and smearing of cells on a monolayer). When cellular, smears revealed spindle or polygonal singly dispersed cells with bland, plump nuclei, as typically described in the literature13 (Figure 6). Longitudinal nuclear grooves of the nuclear membranes were not identified. More than 50% of cells were positive for factor VIII and CD34.

All patients were treated with superficial field radiotherapy with 60Co gamma rays. For the floor of mouth lesions, a central 8- × 8-cm field was used, with a total administered dose of 38 Gy fractionated over 16 days in 12 fractions of 150 cGy. For the first hard palate lesion (type III), 2 fields were used (frontal 7 × 4 cm and lateral 4 × 4 cm), each receiving a total dose of 1260 cGy given in 7 fractions of 180 cGy over days. The second hard palate lesion (type I) received an initial total dose of 30 Gy in 15 fractions of 200 cGy over 24 days, and an additional course of 16 Gy in 8 fractions of 200 cGy over 9 days. Severe mucositis was observed in 1 patient and was managed according to protocol. Treatment resulted in com-
plete remission in all patients. The total administered doses were similar to previously reported, typically curative due to the known radiosensitivity of the tumor. Patient follow-up was 2 to 38 months. All patients were disease-free on last follow-up, except for the patient with the renal transplant who had suspicious areas on the right medial tibial surface, and remained on observation.

**Non-AIDS Kaposi’s Sarcoma in the Head and Neck Area.** We reviewed the literature from both before and after the onset of the AIDS epidemic, when the incidence of head and neck Kaposi’s sarcoma significantly increased. Both limited (case reports, series, review articles) and unlimited searches were performed with a combination of relevant MeSH terms (“Kaposi’s sarcoma,” “oral,” “head,” “neck,” “head and neck,” “transplant”) using the MEDLINE and EMBASE databases.

A limited number of review articles focus on the incidence of Kaposi’s sarcoma in the head and neck area outside the well-characterized occurrence in HIV-positive individuals. Most reviews, however, mainly focus on the oral cavity lesions rather than head and neck in general. All non-AIDS Kaposi’s sarcoma cases involving the head and neck area were documented, including the nose, eyes, ears, and larynx. We identified 251 non-AIDS head and neck Kaposi’s sarcoma cases including our 3 cases (reference list too extensive to be fully cited). Patient age ranged from 22 to 80 years, with an average age of 55.9 years (SD, 16.15 years). The men-to-women ratio was 3.6:1, significantly different to the reported 17:1 ratio for type I Kaposi’s sarcoma in general. The sublocalization of the lesions within the head and neck area is presented in Figure 7 (lesions in different head and neck sites in the same patient are considered separately). In our review of the literature, the commonest sites of presentation (where site was specified) were the palate (hard and soft) and the oropharynx (including the tonsilar fossae), also being the commonest sites reported in the literature. The increased incidence of auricular lesions noted in our review (11.6%) actually reflects 2 large published series. The fact that the ear did not feature, with comparable incidences, in previous reviews is probably because, as mentioned earlier, they mostly focused on oral cavity/mucosal involvement. Unusual sites of presentation included the salivary glands (0.7%), scalp (1.1%), and buccal mucosa (1.1%). Overall, 23 patients (9.16%) had multiple head and neck Kaposi’s sarcoma lesions on presentation. There were 53 cases (21.11%) of primary head and neck Kaposi’s sarcoma, 31 of which (12.35%) were located in the oral cavity (mainly initial presentation followed by lesions elsewhere, while some cases were sole manifestation). It should be noted that the figures on primary and multiple lesions represent only documented cases, as cases with missing data were not included in the estimation.

It is of note that laryngeal Kaposi’s sarcoma lesions seem to be almost always associated with classical skin lesions, and that the majority of head and neck cases were reported to be associated with simultaneous skin involvement of other regions in 84%. With regard to type III Kaposi’s sarcoma lesions, these occur mainly in patients with renal transplant but also in patients with other transplants (eg, cardiothoracic, liver transplant), as well as after immunomodulatory treatment for other conditions (eg, Hodgkin’s disease). Kapo- si’s sarcoma lesions in these patients are reported to be of a higher incidence compared with the general population, the difference ranging from 150 to 200 times, to even a 500- to 1000-fold increase, with large racial ethnic variation. It is actually estimated to be the fourth most common posttransplant malignancy (4%). Interestingly, it presents in the same ethnic groups as types I and II Kaposi’s sarcoma; however, the men-to-women ratio is 3:1 in contrast to the reported 17:1 ratio in type I Kaposi’s sarcoma. The average time for Kaposi’s sarcoma development following transplantation is 21 months. Disease course and aggressiveness depends on the degree of immunosuppression, and frequently regresses following modification or discontinuation of immunosuppression. Alternatively, radiotherapy may be carefully used for lesions of

**FIGURE 7.** Kaposi’s sarcoma in the head and neck area: lesion distribution. KS, Kaposi’s sarcoma; ns, nonspecified. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
the oral cavity or the skin.\textsuperscript{9} We identified 20 reports (including our own) of type III Kaposi's sarcoma,\textsuperscript{12,22,23,28–36} including 1 incidence of oral Kaposi's sarcoma with concurrent tuberculosis.\textsuperscript{34} The average age of the patients was 48.4 years (SD, 13.75). The men-to-women ratio was 2:1. Sixteen of 20 cases (80\%) were primary lesions, and in 5 cases (25\%) there were multiple head and neck lesions on presentation. As with our case, cyclosporine and costicosteroid combination is reported to have stronger association with development of Kaposi's sarcoma lesions\textsuperscript{7} compared with azathioprine and prednisolone (0.87\% of patients with renal transplant under cyclosporin treatment).\textsuperscript{24,37} This is possibly due to the inhibitory effect of cyclosporin on T-helper cells.\textsuperscript{30} This also indicates the reason for the biological similarity between cyclosporin-related type III Kaposi's sarcoma and AIDS-Kaposi's sarcoma, reflecting on both tumor aggressiveness and similar intracytoplasmic abnormalities.\textsuperscript{30}

Another interesting feature is that in previous decades (prior to the 1980s) Kaposi's sarcoma was found to be associated with numerous conditions of abnormal immune response (immunodeficiencies, hypogammaglobulinemia, multiple myeloma, lymphoblastic leukemia, lymphangioma, chronic lymphocytic leukemia, autoimmune hemolytic anemia).\textsuperscript{38} A percentage of these cases, however, might represent undiagnosed HIV cases.

It is worth noting that the small number of reported cases might be the result of inaccurate histopathological diagnosis. It could also be the result of little interest in the recording of the head and neck cases, especially for patients with type III Kaposi's sarcoma.

\section*{DISCUSSION}

\subsection*{Pathogenesis.} The lesion is associated with a rhadinovirus, the human herpesvirus 8 (HHV8; previously termed Kaposi's sarcoma associated herpesvirus, KSHV), identified in 1994.\textsuperscript{39,40} The complete HHV-8 genome sequence shows that it has sequence similarities to other gammaherpesviruses including herpesvirus saimiri (HVS), murine gammaherpesvirus 68 (MHV68), and Epstein–Barr virus (HHV-4). The approximately 165-kb genome contains over 80 open reading frames arranged in a long unique region flanked by multiple 801-bp terminal repeat units of high G+C content. The long unique region contains blocks of conserved genes found in most herpesviruses, interspersed with blocks of nonhomologous genes that are specific for HHV-8 and related viruses.

HHV8 deoxyribonucleic acid sequences were found in approximately 95\% of Kaposi's sarcoma lesions and more than 50\% of peripheral blood cells in both patients with AIDS and non-AIDS Kaposi's sarcoma, not related to age, sex, race, and geographic distribution.\textsuperscript{41,42} In contrast, it was rarely detected in normal skin biopsies of such patients and completely absent from control tissues of healthy individuals. HHV8 seroprevalence is indeed a predictive marker for Kaposi's sarcoma development.\textsuperscript{3,7,43} HHV8 encodes homologues of human cellular proteins involved in cell cycle regulation, cell proliferation, apoptosis, angiogenesis, and immune regulation. Most of the spindle and endothelial cells are latently infected, with a small subpopulation supporting lytic viral growth.\textsuperscript{7} With regard to genotype, the classical Mediterranean samples are reported to be prototype A strains, whereas in Africa the B and C strain subgroups are predominant.\textsuperscript{44}

Pathogenesis of Kaposi's sarcoma is now recognized to be multifactorial. Kaposi's sarcoma initiation involves activation of CD8+ T cells and expression of Th1 inflammatory cytokines such as interferon-gamma (IFN-\(\gamma\)), interleukin 1\(\beta\) (IL-1\(\beta\), and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)). These promote reactivation of HHV8 and activation of endothelial cells to acquire the spindle-shaped phenotype and produce angiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Kaposi's sarcoma progression is associated with the long-term expression of HHV8 latency genes such as latent nuclear antigen (LANA), viral cyclin D (v-cyc D; ORF 72), viral flice inhibitory protein (v-FLIP; open reading frame [ORF] K13), kaposin (ORF K12), and the deregulated expression of oncogenes or oncosuppressor genes (c-myc, Bcl-2, p53). This latter “molecular piracy” may help the virus to evade immune responses, prevent cell cycle shutdown, and interrupt activation of apoptotic pathways. In addition, the HIV-1 Tat protein acts as a progression factor for AIDS-Kaposi's sarcoma by stimulating Kaposi's sarcoma growth, angiogenesis, and migration/invasion, the latter by upregulation of matrix metalloproteinases expression.\textsuperscript{3,7} Therefore, it might be that Kaposi's sarcoma lesions progress from an early-stage polyclonal reactive-inflammatory-angiogenic hyperplastic process to a monoclonal true sarcoma in later stages. Furthermore, there is evidence that a milieu of immunosuppression (such as occurring
in HIV-affected individuals and patients with transplant) supports HHV8-induced Kaposi’s sarcoma progression, and is hence associated with more aggressive forms of the disease.\(^7\)

**Histopathology.** For all Kaposi’s sarcoma types, 3 phenotypic stages (patch, plaque, nodular) are recognized, with corresponding progressive histopathology characterized by perivascular and interstitial spindle cell proliferation, angiogenesis, inflammatory cell infiltrate, and edema.\(^7,45\) The precise lineage relationship of Kaposi’s sarcoma is still uncertain. Endothelial cells of vascular or lymphatic origin are considered the cells of origin. However, the spindle-cell compartment is heterogeneous, and despite the fact that Kaposi’s sarcoma-derived spindle cell lines have been found to produce collagenases and exhibit invasive potential in vitro, they failed to produce malignant tumors in immunodeficient mice, highlighting the controversy on the definition of Kaposi’s sarcoma as a true neoplasm versus a reactive process/hyperplasia, at least at its early stages. This is further enhanced by the fact that Kaposi’s sarcoma lesions can simultaneously appear at different sites with symmetrical or dermatome distribution and can regress spontaneously or following therapy.\(^3,7,45\)

**Cytopathology.** Diagnosis by aspiration cytology is possible, and the aspirate may reveal composite rafts or tangles and singly dispersed individual cells. The cells are spindle or polygonal with bland, plump nuclei without hyperchromatism, sometimes with characteristic longitudinal nuclear grooves or infoldings of the nuclear membrane. Diagnostic intracytoplasmic bodies that represent altered ingested red cells might be identified. Mitoses are few. Hemosiderin granules may be found in accompanying macrophages.

If found, these spindle cells indicate proliferated endothelial cells which can be confirmed by immunocytochemistry, eg, for factor VIII or cluster of differentiation antigen 34 (CD34).

**HHV8 in the Diagnosis of Kaposi’s Sarcoma.** HHV8 has been proposed as a differential diagnostic marker for all Kaposi’s sarcoma types.\(^46,47\) HHV8 detection methods include HHV8 immunohistochemistry,\(^47,48\) polymerase chain reaction (PCR) detection either nested,\(^39,40,48,49\) solution phase,\(^45\) or real-time quantitative PCR,\(^43,50,51\) reverse transcriptase (RT)-PCR,\(^52\) PCR in situ hybridization,\(^43,50\) in situ RNA hybridization,\(^50\) or HHV8 serology.

On a differential diagnostic level, HHV8 positivity allows distinction of the early-stage lesions from inflammatory dermatosis or angiodermatitis,\(^47\) and of the late-stage lesions from pyogenic granuloma, spindle-cell hemangioendothelioma (pseudo-Kaposi’s sarcoma, usually associated with Klippel–Trenaunay syndrome), kaposiform hemangioendothelioma, hemangioepithelioma, angiosarcoma, fibrosarcoma, bacillary angiomatosis, and other arteriovenous malformations.\(^8,47,53\) HHV8 immunohistochemistry offers the advantage of a fast, low-cost, and readily available diagnostic technique, particularly useful in ambiguous lesions where the characteristic histological features of Kaposi’s sarcoma may not be well developed. In these early-stage lesions it can aid laboratory Kaposi’s sarcoma diagnosis, possibly in combination with VEGFR-3 immunohistochemistry.\(^54\)

HHV8 is also found in other AIDS-related conditions, such as multicentric Castleman’s disease (MCD), a lymphoproliferative disorder, alone or in the context of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes),\(^48,49\) and body cavity-based lymphoma/primary effusion lymphoma, a condition of lymphomatous effusions in cavities/serous membranes without mass formation, belonging to AIDS-NHL (non-Hodgkin’s lymphoma).\(^3,43,54,55\) MCD has also been reported in patients with non-AIDS receiving immunosuppressive treatment, also associated with HHV8 expression.\(^37\)

Anti-HHV8 therapy can be used for both treatment and prophylaxis of Kaposi’s sarcoma, mainly so in the HIV-positive patients who constitute a high-risk group.\(^7\) The fact that HHV8 appears to be transmitted via mucosal shedding\(^50\) may explain both the increased transmission in homosexual men (oral exposure to infectious saliva), and the increased percentage of oral cavity lesions in AIDS-Kaposi’s sarcoma.

**Management.** Kaposi’s sarcoma management depends on the type, extent/dissemination of lesions, and organs involved. Local treatment modalities are surgical and laser excision, cryotherapy, radiotherapy, intralesional vinblastine or vincristine injections, and topical application of vinca alkaloids, bleomycin, or retinoids. Experimental local therapy includes injections of interferon-α (IFN-α), human choric gonadotrophin, granulocyte macrophage colony stimulation factors, and recombinant interleukin-2. Systemic
therapy includes highly active antiretroviral therapy (HAART) ± IFN-α for minimal and/or indolent cutaneous disease and chemotherapy (paclitaxel, ABV [doxorubicin, bleomycin, vincristine], vincristine + bleomycin, liposomal anthracyclines) for rapidly progressive/visceral disease. Pathogenesis-based therapies include angiogenesis inhibitors, thalidomide, antisense oligonucleotides directed against angiogenic growth factors, cellular protease inhibitors, HIV protease inhibitors, retinoic acids, and anti-HHV8 therapy. 3,7,9,56

Especially for oral cavity Kaposi’s sarcoma, radiotherapy is the consensus modality, with reported complete remission of more than 85%. 7,14 A fractionated regime of 1 to 5 Gy doses to a total dose of 15 to 45 Gy is used to minimize complications such as mucositis. 7

CONCLUSION

Non-AIDS Kaposi’s sarcoma infrequently occurs in the head and neck. HHV8 is useful as an adjunct diagnostic tool in such cases. In addition to the classic cases, Kaposi’s sarcoma seems to have an increased incidence in transplant recipients, with head and neck cases representing a significant percentage, both as cutaneous and mucosal involvement. 52 A closer collaboration between transplant teams and maxillofacial surgeons/oral pathologists would help toward early identification of these cases, as well as offer insight in the biological characteristics of the disease in association with conditions of immune deficiency.

REFERENCES


