

Kaposi Sarcoma of Major Salivary Gland Origin

A Clinicopathologic Series of Six Cases

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BACKGROUND. Kaposi sarcoma (KS), one of the defining tumors of acquired immune deficiency syndrome (AIDS), is rarely identified in the major salivary glands. To the authors' knowledge, no previous published series has evaluated the clinicopathologic aspects of this tumor in major salivary glands.

METHODS. Six cases of salivary gland KS, diagnosed between 1970 and 1998, were retrieved from the files of the Oral and Maxillofacial Pathology Registry of the Armed Forces Institute of Pathology. Histologic features were reviewed and special stains, immunohistochemical studies, and in situ hybridization were performed (n = 4). Patient follow-up data were obtained.

RESULTS. The patients included 6 men ages 20–73 years (average, 53.0 years). Patients presented clinically with a mass in the submandibular (n = 4) or parotid (n = 2) gland region. Symptoms were present for a mean of 13.7 months. The tumors measured 1–4 cm (average, 2.5 cm) in greatest dimension. Histologically, the tumors exhibited the usual features of KS: a spindle cell vascular proliferation arranged in fasciculated bundles, variable nuclear pleomorphism, mitotic figures, extravasated erythrocytes, and hyaline globules. Five patients were serologically positive for human immunodeficiency virus (HIV) (three homosexual males, one infected by a contaminated blood transfusion, and one with an unknown risk factor). Human herpesvirus-8 (HHV-8) was present in all cases tested (n = 4). Patients were treated with surgical excision (n = 6), followed by chemotherapy (n = 1) for the single patient with other foci of KS (rectal). Three patients died of AIDS-related infectious complications and one of congestive heart failure, whereas the remaining patients are alive with AIDS but free of salivary gland KS.

CONCLUSIONS. Salivary gland enlargement is frequently identified in HIV positive or AIDS patients. Although rare, it is important to consider KS in the differential diagnosis of other AIDS-related salivary gland manifestations (infections and tumors). *Cancer* 2000;88:15–23. © 2000 American Cancer Society.

KEYWORDS: Kaposi sarcoma, salivary gland, immunohistochemical, human herpesvirus-8.

Moritz Kaposi originally described multiple, slowly progressing, pigmented skin plaques in Mediterranean men as a vasoformative lesion that now bears his surname.¹ Since his original description, four forms of the disease have been suggested: epidemic acquired immunodeficiency syndrome (AIDS) form, iatrogenic immunocompromised transplant form, endemic African form, and sporadic form.² These forms can be either mucocutaneous or lymph nodal. There has been a strong association of Kaposi sarcoma (KS) with patients infected with human immunodeficiency virus (HIV) as part of epidemic AIDS. This type of KS has experienced a remarkably increased prevalence.³

Although a number of different salivary gland disorders have an

TABLE 1
Immunohistochemical Panel

| Antigen | Primary antibody | Company | Dilution | Antigen recovery |
|---|------------------|--|----------------|--------------------|
| Vimentin (V9) | MM | BioGenex Laboratories (San Ramon, CA) | 1:400 | Microwave recovery |
| Factor VIII R-Ag | RP | Dako (Carpinteria, CA) | 1:1600 | Enzyme digestion |
| CD31 (JC/70A) | MM | Dako | 1:40 | Enzyme digestion |
| CD34 (QBEnd/10) | MM | BioGenex Laboratories | 1:40 | Microwave recovery |
| Desmin (D33) | MM | Dako | 1:100 | None |
| Smooth muscle actin (1A4) | MM | Sigma Chemical (St. Louis, MO) | 1:800 | Enzyme digestion |
| S-100 protein | RP | Dako | 1:400 | Enzyme digestion |
| Factor XIIIa | MM | Calbiochem (San Diego, CA) | 1:2000 | Enzyme digestion |
| Glial fibrillary acidic protein | RP | Dako | 1:2000 | Enzyme digestion |
| Cytokeratin cocktail (AE1/AE3 and CK-1) | MM | Boehringer Mannheim (Indianapolis, IN) and Dako | 1:50 and 1:200 | Enzyme digestion |

MM: mouse monoclonal; RP: rabbit polyclonal; R-Ag: related antigen.

increased association with HIV infection and AIDS specifically (severe and recurring protozoal, fungal, bacterial, viral, and opportunistic infections; lympho-epithelial cysts; diffuse interstitial lymphocytosis syndrome; malignant lymphoma⁴⁻⁹), salivary gland KS is rare. Whereas KS has been reported in many different head and neck locations, including mucosal sites,¹⁰⁻²¹ there have only been three reported cases of proven salivary gland KS²⁰⁻²² excluding a few reports of intraparotid lymph node KS.^{14,16,17,23-25} These case reports individually serve as a valuable adjunct to the understanding of HIV infection-associated lesions of the salivary gland. However, a more comprehensive analysis encompassing the use of clinical, histologic, immunophenotypic, molecular (human herpesvirus type 8 [HHV-8]), and follow-up information applied to a group of salivary gland KS, to the best of our knowledge, is absent from the literature (MEDLINE 1966-1999). Therefore, we undertook a study of six cases of KS of the salivary gland to enumerate these various characteristics in a single comprehensive study and to compare our findings with a review of the literature.

MATERIALS AND METHODS

Six cases of salivary gland KS were identified in the files of the Oral and Maxillofacial Pathology Registry at the Armed Forces Institute of Pathology from 1970 to 1998. These six cases were identified in a review of 12,046 (0.05%) benign or malignant primary salivary gland tumors seen in consultation during this same time period. For inclusion in this study, complete clinical information was necessary. Materials within the Institute's files were supplemented by a review of the patient demographics, symptoms at presentation, past medical history, and laboratory data (including HIV status). In addition, we reviewed operative and surgical pathology reports and obtained information

from oncology data services by written questionnaires or oral communication with the treating physician(s). All cases were obtained from civilian sources.

Hematoxylin and eosin-stained slides for all cases were reviewed. All of the cases met the histologic criteria of KS as described by Enzinger and Weiss.² The histologic criteria included, but were not limited to, a vasoformative tumorous proliferation of spindled cells with mitotic figures interspersed with extravasated erythrocytes and demonstrating intracytoplasmic hyaline globules. KS is divided further into clinical types: classic form, epidemic AIDS form, sporadic form, and lymphadenopathic and transplant associated form. Patients who had angiosarcoma, lobular capillary hemangioma, hemangioma, nodular fasciitis, or bacillary angiomatosis were excluded from this study, because we believe that those tumors are distinct entities and are separated by clinical and histologic review from KS.

Formalin fixed, paraffin embedded tissue sections were stained with periodic acid Schiff (PAS) (with and without diastase digestion) and reticulin stain (Manuel method). Paraffin blocks or unstained slides were available in four cases for immunophenotypic analysis according to the standardized avidin-biotin method of Hsu et al.²⁶ The analysis was performed on a single block in each case. A panel of commercially available immunohistochemical antibodies was applied (Table 1). When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 M phosphate buffer, pH 7.8, at 37°C. Antigen enhancement (recovery) was performed as required by using formalin fixed, paraffin embedded tissue treated with a buffered citric acid solution and heated for 20 minutes in a calibrated microwave oven.²⁷ After this, the sections were allowed to cool at room temperature

TABLE 2
Patient Demographics and Clinical Characteristics

| Patient no. | Age (yrs) | Gender | Clinical presentation | Duration of symptoms (months) | HIV status | Mode of transmission | Salivary gland location | Right or left | Size (cm) |
|-------------|-----------|--------|--------------------------|-------------------------------|------------|----------------------|-------------------------|---------------|-----------|
| 1 | 20 | M | Mass, fever, pain | 1 | P | Homosexual | S | R | 3.5 |
| 2 | 42 | M | Mass, recently ulcerated | 70 | P | Homosexual | P | L | 1 |
| 3 | 71 | M | Swelling | 2 | N | Unknown | S | L | 2.5 |
| 4 | 65 | M | Mass | 4 | P | Unknown | S | R | 3 |
| 5 | 47 | M | Mass, enlarging in size | 3 | P | Homosexual | S | R | 4 |
| 6 | 73 | M | Mass | 2 | P | Transfusion | P | L | 1 |
| Average | 53 | — | — | 13.7 | — | — | — | — | 2.5 |

HIV: human immunodeficiency virus; M: male; P: positive; N: negative; S: submandibular; P: parotid; R: right; L: left.

in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control. A positive immunoreaction was determined by chromogen deposition within the cytoplasm of the tumoral cells.

HHV-8 was assessed in four cases. Polymerase chain reaction (PCR) amplification for HHV-8 was performed on formalin fixed, paraffin embedded tissues using flanking intron primers and an internal oligonucleotide probe for the KS330 Bam₂₃₃ fragment on DNA containing lysates, using the *Her-2* gene as a control for amplifiable DNA.^{28–30} PCR was performed using three dilutions of the DNA lysate in each case. Cycling conditions were as follows: denaturation at 94 °C for 5 minutes; then 40 cycles at 94 °C, 58 °C, and 72 °C, each for 1 minute; then a final 72 °C extension for 5 minutes. Products were analyzed by gel electrophoresis through a 2.5% agarose gel, stained with ethidium bromide, and then photographed. After staining, the gel was transferred to a nylon membrane, and a Southern blot analysis was performed for both HHV-8 (233 base pairs [bp]) and *Her-2* (241 bp) PCR products using oligonucleotide probes to the primer sets.^{29,30}

RESULTS

Clinical Demographics and Presentation

All of the patients were men ages 20–73 years, with a mean age of 53.0 years, at the time of initial presentation (Table 2). All of the patients presented clinically for evaluation of a mass or swelling of the major salivary gland (n = 6 patients), recently increasing in size (n = 3 patients). Additional symptoms included fever, pain, and ulceration (1 patient each). The symptoms lasted from 1 month to 70 months, with an average of 13.7 months, although there was a median of 2.5 months. Five patients were serologically positive for antibodies to HIV, whereas the results for patient 3

were not available. The proposed risk factors were homosexual activity (n = 3 patients), contaminated blood transfusion (n = 1 patient), and unknown (n = 2 patients). The salivary gland tumors were the first clinical sign of HIV infection in patients 1, 4 and 6.

Clinical Management and Outcome

All patients were treated by complete surgical excision (Table 3). One patient (patient 2) received adjuvant chemotherapy (VinblastineTM) for systemic (gastrointestinal tract, anus, rectum, and integumentary system) KS. The overall survival of the patients seemed to be dictated by the underlying nature of the disease (AIDS) rather than the presence of KS. Three patients died of infectious complications of AIDS an average of 2.0 years after the presentation of the salivary KS, whereas the remaining patient (whose HIV status was unknown, although the biopsy material was HHV-8 positive) died of congestive heart failure 2.0 years after diagnosis of salivary gland KS (Table 3). The two remaining patients are both alive 5.0 years and 2.1 years, respectively, after the diagnosis of salivary gland KS. Both have AIDS, but it is presently controlled by highly active antiretroviral therapy.

Pathology

Macroscopic findings

The tumors were located within the substance of the submandibular (n = 4 tumors) and parotid (n = 2 tumors) glands, three tumors each on the left and right sides (Table 2), and ranged in greatest dimension from 1 cm to 4 cm (average, 2.5 cm). The parotid gland tumors (1 cm), on average, were much smaller than the submandibular gland tumors (3.3 cm), but there were too few cases to determine statistical significance. The excised tumors were characterized as well circumscribed to locally invasive ovoid masses, surrounded by normal to atrophic or inflamed salivary

TABLE 3
Clinical Location, Treatment, and Patient Outcome

| Patient no. | Salivary gland location | HIV status | HHV-8 result | Treatment | Systemic disease | Status | Cause of death | Follow-up (yrs) |
|-------------|-------------------------|------------|--------------|-----------|------------------|--------|--------------------------|-----------------|
| 1 | S | Positive | n/a | Excision | No | D | Infectious | 5.1 |
| 2 | P | Positive | Positive | Excision | Skin and GI | D | Infectious | 0.5 |
| 3 | S | Unknown | Positive | Excision | No | D | Congestive heart failure | 2.0 |
| 4 | S | Positive | Positive | Excision | No | A | n/a | 5.0 |
| 5 | S | Positive | n/a | Excision | No | D | Infectious | 0.5 |
| 6 | P | Positive | Positive | Excision | No | A | n/a | 2.1 |

HIV: human immunodeficiency virus; HHV-8: human herpes virus-8; S: submandibular; P: parotid; D: dead; A: alive; n/a: nonapplicable.

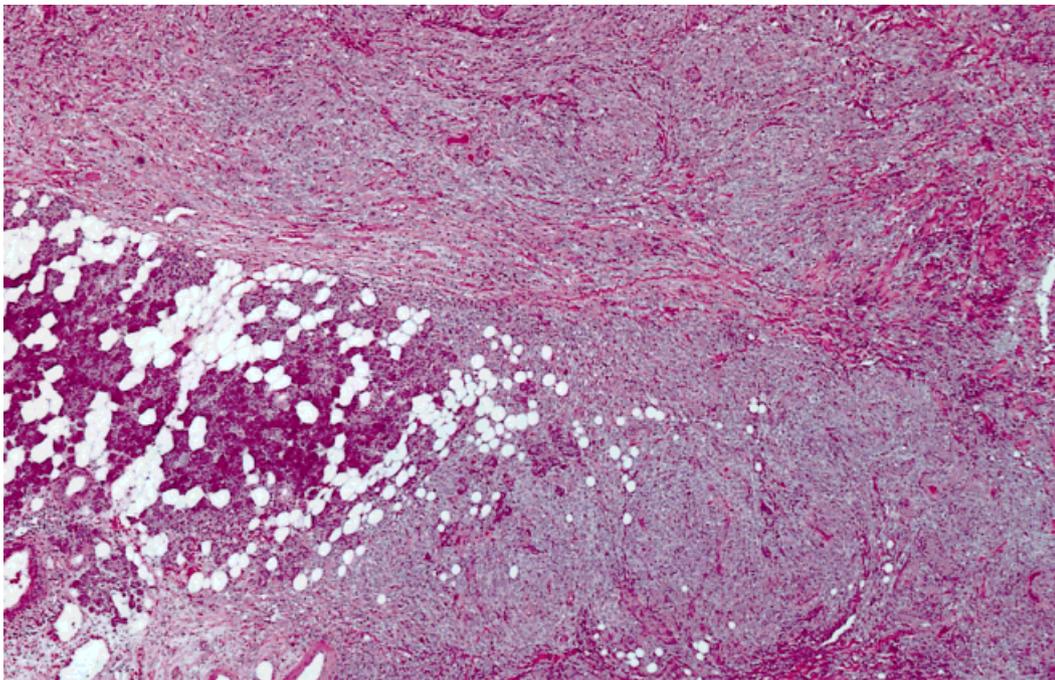


FIGURE 1. Kaposi sarcoma identified invading the salivary gland parenchyma.

gland tissue (Fig. 1). The cut surface of the tumors was fleshy, red-tan, and focally demonstrated fresh and old blood.

Microscopic findings

All of the tumors demonstrated a consistent histologic pattern similar to the plaque-tumor stage KS of cutaneous lesions. The tumors were frequently multinodular on low power magnification. The tumor cells infiltrated into the normal salivary gland with broad, pushing, finger-like growths, following the fibrous bands that separate individual salivary gland lobules (Fig. 1). Invasion into the salivary gland acini was noted but usually was only a focal finding. Occasionally, isolated islands of tumor cells were found within salivary gland parenchyma but distant from the main

mass, suggesting multifocal disease within the affected salivary gland. Furthermore, the tumor cells also were identified invading into intraparotid lymphoid tissue (lymph nodes) when they were present ($n = 3$ tumors).

The patterns of growth of the tumors ranged from compact, coalescing, and sheet-like interlacing fascicles of tumor cells; to transitional areas of larger vascular spaces resembling angiosarcoma; to a sieve-like vasoformative pattern. However, anastomosing vascular channels were not a feature of the tumors. The neoplasms were composed of a monomorphic population of spindled cells interlacing with one another (Fig. 2). Irregular vascular channels were lined by plump endothelial cells supported by an inconspicuous reticular to fibrotic supporting framework. The

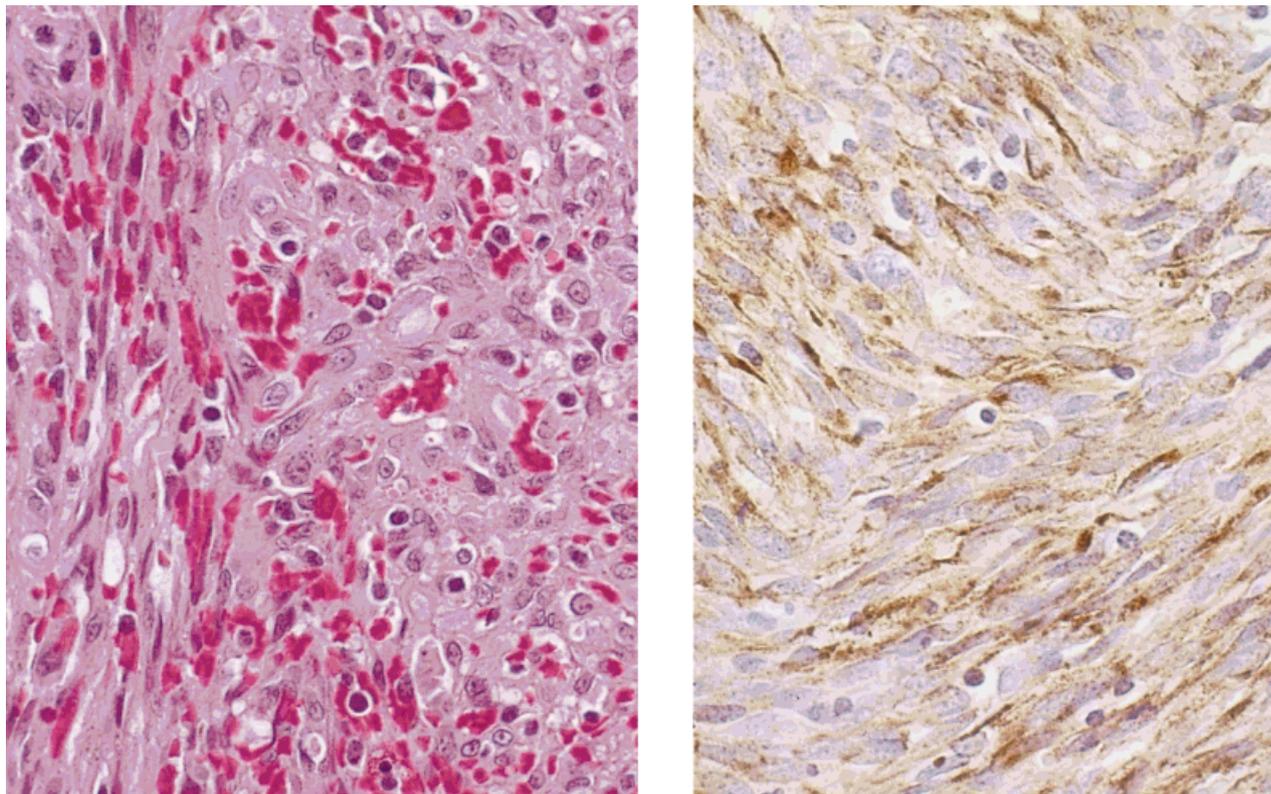


FIGURE 2. Interlacing fascicles of spindled tumor cells. Extravasated erythrocytes are noted in the slit-like vascular channels, whereas hyaline globules are present in a few of the open channels (left). The vasoformative neoplastic cells are decorated by antibodies to factor VIII-related antigen (right).

nuclei were irregular in size and shape, although they were fairly uniform with one another. The nuclear chromatin was vesicular and cleared in areas, whereas it was more hyperchromatic in others (Fig. 3). Mitotic figures were identified easily, including atypical forms. Extravasated erythrocytes were abundant within the slit-like vascular spaces, usually coupled with hemosiderin pigment (Figs. 2, 3). Characteristic (although not pathognomonic) eosinophilic, glassy-hyaline globules were found both intracellularly and extracellularly in all cases (Figs. 2, 3). These globules were accentuated further by applying PAS stain with diastase.

Immunohistochemical results

Although it was not necessary for the diagnosis of KS, a diverse panel of immunohistochemical antibodies (Table 4) was performed to quantify the immunophenotype of the neoplasm, with four cases having sufficient material for study. All of the cases reacted with factor VIII-related antigen (Fig. 2), CD31, CD34, and vimentin, confirming the vascular origin of the tumor. The intensity of the reactions was accentuated with these antibodies in the cytoplasm and at the periphery

of the cells. As expected for a vasoformative neoplasm, there was no tumor cell immunoreactivity with smooth muscle actin, factor XIIIa, desmin, glial fibrillary acidic protein, S-100 protein, or keratin.

Molecular results

All cases tested ($n = 4$ patients) demonstrated HHV-8 (Table 3). Curiously, of the four patients who were positive (patients 2, 3, 4, and 6), patient 3 had an unknown HIV serology; thus, obviously, the mode of transmission was unknown.

DISCUSSION

Since the initial reports of a symptom complex primarily affecting homosexual men,^{31,32} HIV infection followed almost inevitably by AIDS has become a major health care epidemic. There are currently (1997) 28.3 million people living with HIV/AIDS throughout the world, of whom 270,000 are in North America (Centers for Disease Control HIV/AIDS Surveillance Supplemental Report, 1999). These figures represent an increase of 10% over those of 1996, showing that there is still a marked increase in the disease each year. There are a number of AIDS-defining diseases,

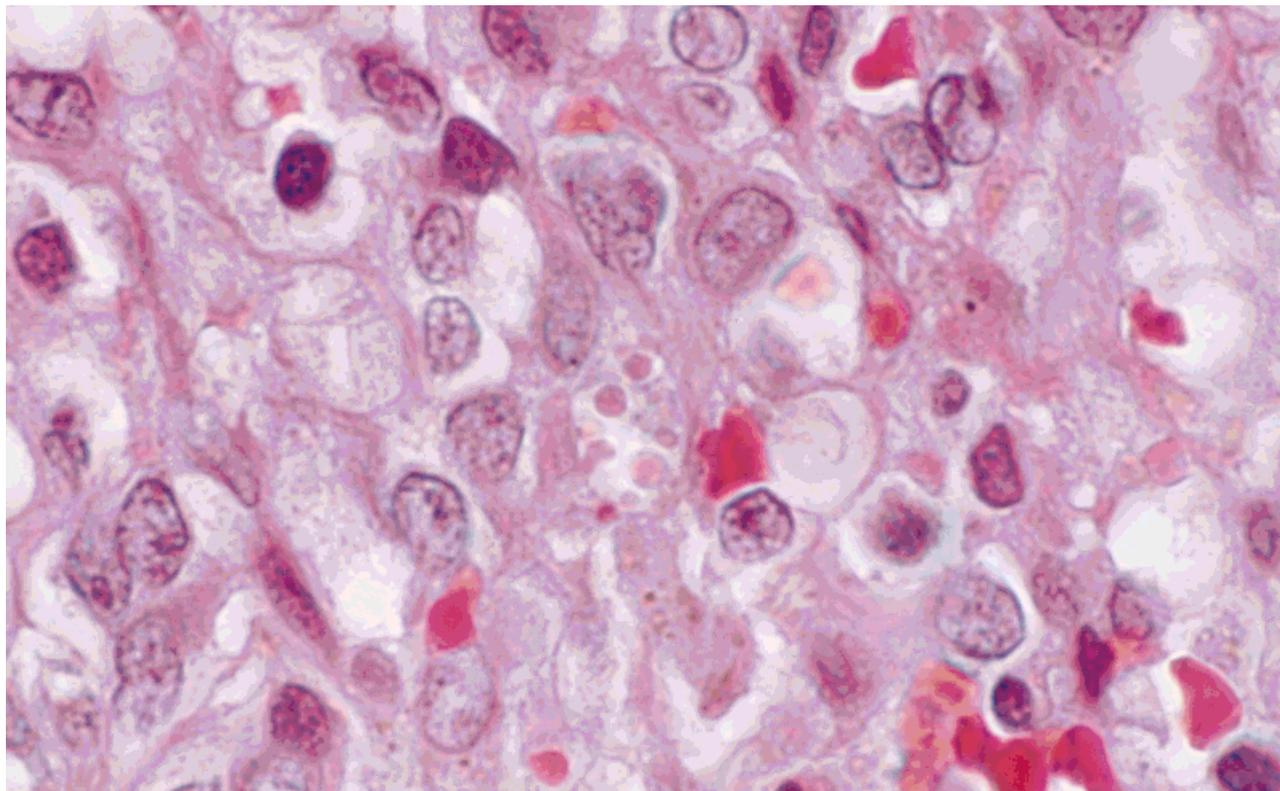


FIGURE 3. Hyaline globules are noted in the center of the field. Focal hemosiderin pigment is noted below the globules. There is only minimal nuclear pleomorphism.

TABLE 4
Immunohistochemical Findings

| Immunohistochemical antibody | Positive reactions |
|------------------------------|--------------------|
| Factor VIII-related antigen | 5 of 5 |
| CD31 | 5 of 5 |
| CD34 (QBend/10) | 5 of 5 |
| Vimentin | 5 of 5 |
| Smooth muscle actin | 0 of 5 |
| Factor XIIIa | 0 of 5 |
| Desmin | 0 of 5 |
| GFAP | 0 of 5 |
| S-100 protein | 0 of 5 |
| Cytokeratin | 0 of 5 |

GFAP: glial fibrillary acidic protein.

including malignancies, of which KS is one of the more specific. A recent study showed that the 10-year probability of developing KS was 49.6% in men affected with both HIV and HHV-8.³³ Therefore, KS is more likely to be included in the differential diagnosis of a variety of head and neck and, more specifically, salivary gland presentations of HIV-infected and AIDS patients.

Salivary gland enlargement seems to have a much

greater rate of frequency in children, although the results are mixed.^{34,35} In the setting of HIV or AIDS, 19% of children and 0.8% of adults present clinically with salivary gland enlargement caused by a wide variety of infectious, reactive, and neoplastic entities.^{34,36} Salivary gland enlargement typically is an early development in the course of AIDS, often presenting as bilateral disease accompanied by cervical lymphadenopathy.³⁷ The most frequently reported disease is multiple lymphoepithelial cysts.^{34,38-44} As clinical awareness of salivary gland manifestations of HIV or AIDS has increased, especially when parotid disease is the first clinical manifestation of HIV infection,⁴⁵ there have been a number of reports in the literature of KS in lymph nodes within or near major salivary glands.^{16,17,21,23-25} However, there are only three reported cases of salivary gland parenchymal KS.²⁰⁻²²

All of our cases occurred in men, with an average age at presentation of 53 years, older than the patients reported in the literature (32 years²¹ and 31 years,²⁰). However, none of the reported cases, including our series, have demonstrated KS of the salivary gland in female patients. The current review of cases spanned

the period 1970–1998; however, the first documented case was diagnosed in 1983, coincident with the time frame during which HIV and AIDS were beginning to be defined better. This finding lends support to the association of KS of the salivary gland with the epidemic AIDS form rather than occurring as part of the iatrogenic immunocompromised transplant form, the endemic African form, or the sporadic form.

Although three of our patients were homosexual, and one patient was infected through a contaminated blood transfusion, other risk factors for KS include immunosuppression, intravenous drug abuse, and hemophilia. We were unable to identify a mode of transmission in two of our patients and were unable to question directly the one patient who died and for whom there was no documented serum HIV antibody result. Although most of the patients reported in the literature with KS in the salivary gland or salivary gland lymph nodes have immunosuppression of one kind or another,^{16,17,20–22,24} there are a few reports of patients with KS within the salivary gland or salivary gland lymph nodes for whom there was no documented immunocompromised state.^{23,25}

Salivary gland diseases have been identified as the primary presentation of HIV or AIDS,⁴⁵ but there have been no documented cases of salivary gland KS as the initial presentation of HIV or AIDS, as occurred in three of our patients (patients 1, 4, and 6). The first patient was identified in 1983 at about the time HIV and AIDS were being defined. Although this first patient died of AIDS-related disorders, it is interesting to note that our three patients who developed salivary gland KS as their initial presentation of HIV or AIDS have survived for a longer time (5.1 years, 5.0 years, and 2.1 years, respectively) than the three patients with other manifestations of HIV or AIDS at initial presentation of salivary gland KS (0.5 years, 2.0 years, and 0.5 years, respectively).

The histologic features of KS are well described, and there are no major diagnostic differential diagnoses for KS of the salivary gland. Sarcomas of the major salivary gland are uncommon,^{46,47} usually manifesting as malignant fibrohistiocytomas or peripheral nerve sheath tumors. Malignant lymphoma is a consideration based on the clinical manifestations of the patient, but it is not a histologic consideration for KS.

“Kaposi sarcoma-associated herpesvirus” (KSHV), renamed HHV-8, is believed to play an etiologic role in the development of KS in patients either with or without evidence of HIV infection.^{29,48–51} HHV-8 also is believed to be transmitted sexually⁵² and to precede the development of KS.^{50,53} Additional studies have shown that antibodies to HHV-8 are present in approximately 80–90% of patients with KS.^{53–55} Our in

situ hybridization results support these findings by demonstrating the presence of HHV-8 in 100% of our tested samples localized to the tumor cells as well as the immediately adjacent lymphoid and salivary gland tissues. We did not obtain nonsalivary gland tissue in which to test further the patient’s HHV-8 findings. It is interesting to note that HHV-8 sequences have not been identified in other vascular tumors.²⁸

Patients who are both HIV positive and HHV-8 positive, as stated above, have a 49.6% chance of developing KS. Therefore, because KS of the head and neck area is quite common,⁵⁶ there should be an increased index of suspicion for KS of the salivary gland when these patients present with salivary gland enlargement.

Death rarely is related directly to KS: Instead, patients with KS in the epidemic AIDS form usually succumb to infectious complications of AIDS. Therefore, when KS of the salivary gland is the initial presenting disease of HIV or AIDS, it may be prudent to thoroughly exclude active or latent infections in other anatomic sites to implement appropriate early therapy.

In summary, salivary gland KS is a rare manifestation of epidemic AIDS, occurring in male patients of any age who usually have documented HIV or HHV-8 antibodies. Salivary gland enlargement should prompt an evaluation, which, in the appropriate clinical setting, may require an open biopsy to prove an etiology for the enlargement. The histologic features of KS are characteristic and are supported further with vascular immunohistochemical antibodies (factor VIII-related antigen, CD31, and CD34). HHV-8 sequences are present within salivary gland KS, as they are in KS of other anatomic sites.⁵⁷ Complete surgical excision is suggested followed by management of the patient’s underlying AIDS diseases.

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