Kaposi Sarcoma with Mucocutaneous Involvement in French Guiana: An Epidemiological Study between 1969 and 2019

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Data on Kaposi sarcoma in French Guiana are scarce and out of date. This territory presents unique epidemiological features. The objectives of this retrospective study were to analyse the clinical features, outcome and incidence of the different forms of Kaposi sarcoma in patients diagnosed between 1969 and 2019. The study population comprised a total of 52 patients. Classical forms included epidemic Kaposi sarcoma (n=30), endemic (n=18), iatrogenic (n=2), classic (n=1) and unclassified Kaposi sarcoma (n=1). The mean annual incidence rate of epidemic Kaposi reached a peak in the 1990s (0.93/100,000) then decreased in the 2000s (0.33/100,000), while the incidence of endemic Kaposi sarcoma reached a peak in the 1980s (0.82/100,000) before decreasing in the 2000s (0.12/100,000). Factors associated with the epidemic form were: sexual intercourse between men (p=0.0054) and Haitian origin (p=0.035). The presence of nodules and/or tumour, lesions limited to the lower limbs, and age >65 years were associated with the endemic form. While Creole populations seem to be as affected by endemic Kaposi sarcoma as their African counterparts, the dynamics of Kaposi sarcoma in French Guiana are now dominated by the epidemic form.

Key words: Kaposi sarcoma; HIV; French Guiana; HHV8; Amerindians; epidemiology.

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Data on KS in French Guiana are scarce and out of date (3–7). The first case of KS was described in 1948 (3), but the lack of a dermatologist in the territory did not allow the diagnosis of other cases until 1969. The evolution of the management and diagnosis of KS in this territory has not been studied. Given the epidemiological features described in other countries, one could expect a sharp rise of incidence at the peak of the HIV pandemic, then a decrease with the introduction of highly active antiretroviral therapy (HAART) (8, 9). In this population with a high prevalence of HIV (10–12), one should also expect an improvement in the treatment and outcome due to the introduction of HAART and the shift from surgery and chemotherapy alone (13, 14). Concerning non-epidemic KS, French Guiana also represents an interesting field of study, as this French overseas territory is inhabited by several different ethnic groups, including Creoles and Maroon peoples (Bushinengue) of original West African ancestry but living in South America for a few centuries, Europeans from mainland France, Asian immigrants, Brazilians of mixed ancestry, and autochthonous Amerindian groups. This complex ethnic composition is likely to challenge the usual classification of classic and endemic KS and to provide fresh data on poorly studied populations, such as Amerindians and Maroons (5–7). A high seroprevalence of HHV8 has been reported in these 2 populations (11.8–13.2%) among Maroon people (5, 6).
and 23% among Amerindians) (5–7), but its influence on the prevalence of active KS has not been studied.

As French Guiana is a French overseas territory, it benefits from a universal, free-for-all healthcare system, including significant care for immigrants. However, due to logistic and geographical issues in this area, which is mostly covered by rainforest, difficulties in access to healthcare are more prominent than in mainland France. The modern healthcare system was put in place progressively in the 1960s. Therefore, this territory represents a unique setting in South America.

The objectives of this study were to analyse the clinical features, outcome and incidence of the different forms of KS in French Guiana since 1969.

**MATERIALS AND METHODS**

This study retrospectively included all patients with cutaneous lesions of KS and/or otolaryngological mucosal involvement diagnosed between 1969 and 2019 at the Dermatology Department of Cayenne Hospital. It is noteworthy that this department is the referral centre for all suspected cases of KS in French Guiana. Patients seen by general practitioners or dermatologists throughout this French territory are always referred to Cayenne Hospital for diagnosis and treatment. There is no other Dermatology Department and no other Histopathology Laboratory in French Guiana. Therefore, this database provides a complete list of all proven KS in French Guiana.

Diagnostic criteria included compatible skin and/or oral mucosal lesions and histopathological features: normal epidermis, increased spindle cells and vascular structures in a network of collagen and reticular fibres of the dermis, extravasated erythrocytes, hemosiderin-laden macrophages and polymorphic inflammatory cell infiltration (15). Since 2010, immunohistochemical stain against HHV8 has been introduced (16). Diagnosis was made by compatible clinical features and confirmed by compatible histology ± immunohistochemistry or positive HHV8 PCR on skin biopsy.

Data extracted from medical files included age, sex, country of birth, localization and type of lesions, extracutaneous involvement, treatment and several laboratory tests at the time of diagnosis. The names of patients with proven diagnosis are prospectively classified in the Dermatology Department of Cayenne Hospital. Medical data were retrospectively extracted for the purpose of this study. This retrospective study was conducted according to the Declaration of Helsinki, and included only data that were collected for routine clinical care. Under French law, no further legal clearance is required for observational retrospective studies. Incidence rates were calculated in relation to the National Institute of Statistics and Economic Studies (INSEE) data for the general population of French Guiana.

**RESULTS**

**Patients’ characteristics**

A total of 52 patients were included in the study, from among 68 patients extracted from the clinical database. Sixteen were excluded: 4 originated from mainland

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*Fig. 1. Clinical presentations of several forms of Kaposi sarcoma (KS).* (a) Patch stage, plaque stage and nodule stage, (b) ocular tumour, (c) hard palate tumour lesion, and (d and e) immune reconstitution inflammatory syndrome in epidemic KS. (f) Malignant transformation: anaplastic KS. (g) Vascular nodules in classic KS. (h) Nodule and tumour (i) nodules in endemic KS. (j) Papules in iatrogenic KS.
France and spent only a few months in French Guiana, 2 patients were lost to follow-up, 5 patients had a different sarcoma and had been misclassified, and 5 presented only extracutaneous lesions. Among these 5 patients, 3 were infected with HIV, and 2 presented lung involvement. Other clinical data were not available.

The study population comprised 52 persons: 43 men and 9 women, with a 1:4.8 sex ratio. Median age was 49 years (range 27–89). Concerning occupations, there were 2 farmers, 1 gold miner, 4 retirees, 7 unemployed people, 3 higher grade professional occupations, 4 lower grade professional occupations, 11 intermediate occupations, 18 routine occupations, and 2 sex workers. Concerning sexual preferences, there were 11 MSM, who all presented an epidemic form of KS. Median follow-up time was 60 months (range 1–348).

Twenty-nine patients died during follow-up. Five died of KS (3 from AIDS-associated KS, 1 from endemic KS, and 1 from anaplastic KS). The other causes of death were diverse (AIDS, cancer, suicide, heart failure, ruptured aortic aneurysm).

Among the 52 patients, 30 patients were classified as epidemic KS, 18 endemic KS, 2 iatrogenic KS and 1 classic KS. One patient remained unclassified and is discussed further below. Concerning comorbidities, 8 patients presented other malignancies, 1 had diabetes mellitus, and 1 had tuberous sclerosis. The clinical picture of each type of KS is shown in Fig. 1. The most frequent places of birth were French Guiana (n = 25 patients), Haiti (n = 7), Europe (n = 7) and Saint Lucia (n = 5) (Table I).

Three patients were from South America (including 2 Brazilians). Only one patient of Maroon ancestry was recorded, a Surinamese man with endemic KS.

Concerning the different types of lesions, the most frequent were nodules (n = 26), followed by papules (n = 14), plaques (n = 12), tumours (n = 10), and macules (n = 8). Cutaneous lesions involved the legs (n = 46), arms (n = 15), trunk (n = 8), head and neck (n = 4), genitals (n = 1), and oral mucosa (n = 2). The lesions were limited to the legs in 25 cases. Extradcutaneous lesions were found in 12 patients (9 of whom had epidemic KS, mostly presenting with gastro-intestinal involvement).

### Variation in incidence rates

The number of new cases reached a peak in the 1990s (18 cases) then decreased in the 2000s.
before a new increase since 2010 (Fig. 2). The mean annual incidence rate per 10-year period per 100,000 inhabitants (Fig. 3) reached a peak in the 1990s (1.41) then decreased in the 2000s (0.5) and has stabilized since the 2010s (0.4).

Comparison between endemic and epidemic Kaposi sarcoma

Clinical and epidemiological features of the 2 main groups, epidemic KS and endemic KS, are compared in Table I. Concerning the distribution patterns of age groups (Fig. 4), epidemic KS was most frequent in patients aged 31–40 years (56.7%), with a median age of 37 years (range 27–78). Conversely, endemic KS was more common among older patients (38.9% in the 71–80-year-old group) with a median age of 69 years (range 46–85). In univariate analysis, MSM ($p=0.0054$) and Haitian origin ($p=0.035$) were associated with the epidemic form of the disease. The presence of nodules and/or tumours in endemic KS (94.4%) was significantly higher than in epidemic KS (53.8%), $p=0.003$. The mean annual incidence rate per 100,000 inhabitants of epidemic KS reached a peak in the 1990s (0.93/100 000 inhabitants) then decreased in the 2000s (0.33) and stabilized in the 2010s (0.34), while that of endemic KS reached a peak in the 1980s (0.82) and decreased continuously through the 2000s (0.12) and 2010s (0.07) (Fig. 3). Although the first cases of epidemic KS in the current study were recorded in 1980, 90% of new cases (27/30) occurred after 1989 (Fig. 2). All MSM patients ($n=11$) and all Haitian patients ($n=7$) presented epidemic KS. Four patients (13%) were diagnosed with KS and HIV simultaneously. The median CD4 level at KS diagnosis was 80/mm$^3$, although 4 patients (13%) had >300 CD4/mm$^3$ at the time of KS diagnosis (Table I).

Description of a rare case of anaplastic Kaposi sarcoma

A 70-year-old man of Amerindian origin was diagnosed in 2012 with nodular, unclassified KS of the lower limbs with gastric involvement. He received several courses of doxorubicin with initial response, then was lost to follow-up, before presenting with extensive, tumoural lesions (Fig. 1f). The histology of tumour progression supported a diagnosis of anaplastic KS (dense masses of relatively undifferentiated epithelioid cells of medium-to-large size, with a high mitotic count and areas of necrosis, positive HHV8 and CD34 immunostaining) and the patient died a few months later.

Histological sections of biopsied materials were assessed in terms of histological type and stage (17). The early patch was defined by inflammatory cells, perivascular dermal lymphocytic infiltrate, a promontory sign, or proliferation of oddly shaped, endothelial cell-lined vascular channels surrounding existing vasculature, without spindle cells. The intermediate plaque was characterized by the presence of scattered spindle cells...
and vascular structures. The late nodule stage presented more spindle cells and blood-filled pseudovessels (Fig. 5). As this patient presented a very specific clinical evolution, was not infected with HIV, and belonged to a community (Amerindian) that is not linked with either classic or endemic KS, we chose to report this case as “unclassified”. Indeed, this case did not entirely fit into any of the KS types.

**Treatments**

Concerning treatments (Table I), the first antiretroviral agent against HIV (zidovudine) in the current study was used in 1990 and the first chemotherapy (interferon) in 1989. Since 1996, 16 patients have been treated with HAART. Among 30 cases of epidemic KS, bleomycin was the main chemotherapeutic drug in 10 cases, followed by doxorubicin (5, including 3 with pegylated lipo-

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**Fig. 5. Histological features in Kaposi sarcoma (KS).**

(a) This image shows the patch stage of Kaposi sarcoma: discrete vascular proliferation dissecting the collagen bundles of the dermis associated with a mild lymphocytic and plasma cells infiltrant and some extravasated red blood cells (Hematoxylin and Eosin stain, x100). (b and c) Endothelial cells of neo-formed angulated vessels show no mitosis or atypia, but express by immunohistochemistry the vascular marker CD34 (IHC CD34 antibody, x100) and HHV8 (IHC HHV8 antibody, x100). (d) Plaque stage of Kaposi sarcoma: there is a more marked vascular proliferation in the dermis and superficial part of the hypodermis, with some spindle cells bordering fine vascular slits containing few red blood cells (Hematoxylin and Eosin stain, x200). (e and f) The endothelial cells of the neo-formed vessels show positive staining by the vascular marker CD31 (IHC CD31 antibody, x400) with nuclear positivity of HHV8 (IHC HHV8 antibody, x400). (g) Nodular stage of Kaposi sarcoma: it is a relatively well circumscribed nodule located in the dermis consisting of massive proliferation of spindle cells delimiting narrow vascular clefts (Hematoxylin and eosin stain, x50). (h) In the nodular stage, spindle cells show mild to moderate atypia but mitoses may be frequent (Hematoxylin and eosin stain, x200). (i and j) Spindle cells strongly express CD34 (IHC CD34 antibody, x400), and most nuclei express HHV8 (HHV8 IHC antibody, x400). (k) Anaplastic variant of Kaposi sarcoma: cellular atypia are marked and mitoses are frequent, with small foci of hemorrhage and necrosis (Hematoxylin and eosin stain, x200). The nuclei of anaplastic tumor cells strongly express HHV8 (IHC HHV8 antibody, x400).
DISCUSSION

KS is probably a solitary or multifocal angiosarcoma of lymphatic origin, initially described as CKS almost 150 years ago, in elderly men of Middle Eastern and Mediterranean descent (1). It is the second most frequent malignant tumour in individuals infected with HIV (18), although it also occurs in HIV-negative individuals. The current study provides the first detailed description of the demographics, clinical features, treatment and prognosis of KS in French Guiana. Concerning the presence of HHV-8 in this territory, seroprevalence studies were carried out in 2 endemic populations (Maroons and Amerindians) in the Western part of the country, but not in the general population (5–7). It is notable that there is no data on seroprevalence in the Creole population, which is the largest ethnic community in French Guiana (5–7).

In other studies in South America (19), HIV-negative KS in Creoles and other peoples of mixed African ancestry were classified as endemic, while cases in people of European ancestry were deemed as classic forms.

The current results confirm these previous findings and show that non-epidemic KS in patients born in French Guiana usually followed the clinical features of endemic KS (predominance of nodules and/or tumour, lesions limited to the lower limbs, older patients). Although African ancestry is often less important in Creole people than in African or African Americans (20, 21), the current data show that their predisposition to endemic KS is similar. However, the clinical profile of endemic KS in French Guiana is closer to the profile of classic KS, a disease located in the lower limbs (90%) and the age of onset is relatively higher than is reported in Africa (22, 23).

Concerning the other forms of KS, 2 patients in this study (3.8%) presented iatrogenic KS, a low figure compared with other studies from Israel (9.6%) (24), Finland (5%) (25) and Spain (9.4%) (9). Lesions of iatrogenic KS are often limited to the skin and usually heal with discontinuation of immunosuppressive therapy (26–28). However, the complete discontinuation of immunosuppression is rarely an option in patients with organ transplant and a significant proportion of patients may need additional chemotherapy (29). In the current study, 1 of these 2 iatrogenic cases was complicated by digestive bleeding, a complication already reported (27). The development of new immunosuppressive treatments in French Guiana could lead to the emergence of iatrogenic KS. Notably, recent cases of iatrogenic KS secondary to anti-tumour necrosis factor alpha (anti-TNFα) have been described (30, 31). As these drugs are likely to be widely used in the coming years in French Guiana, it is useful to keep in mind their potential role in KS.

Classic KS was also very rare, with only 1 case in the current study. A review of published cases in South America in 2005 (19) reported 250 cases across the subcontinent, with significant numbers in Argentina (n = 68), Colombia (n = 79) and Peru (n = 96). The lower proportion in the current study might be explained by different routes of European migration. Most people of European ancestry in Argentina, Colombia and Peru are descended from Spanish immigrants and are expected to present common genetic features with Mediterranean populations in which classic KS is frequent. On the other hand, people of European ancestry in French Guiana descend from settlers from Northern France.

The variation in annual incidences of KS (Fig. 3) shows how the dynamics of this disease in French Guiana have been influenced by the HIV pandemic and the emergence of epidemic KS. The number of patients diagnosed annually reached a peak in the 1990s, mirroring the emergence of AIDS in French Guiana, as reported in similar studies (9, 17, 25, 32). Regarding the incidence rate of epidemic KS, it remained low throughout the 1980s, as the HIV epidemic in French Guiana was not fully established. It reached a peak in the 1990s as the epidemic increased then decreased during the 2000s after the introduction of HAART.

The number of people living with HIV in French Guiana in 2018 was estimated to be 3,800 among a population of 262,381 (11).

In 2016, the prevalence of HIV in the general population of French Guiana was still very high, between 1.18% and 1.35% (12). However, the annual incidence rate of HIV was declining (1.1 per 1,000 in 2001 compared with 0.65 per 1,000 in 2016) and the proportion of patients who are unaware of their seropositivity is thought to be decreasing (11, 12), the lasting effects of the HIV pandemic remain visible in this cohort. Epidemic KS was the most frequent presentation (30/52, 57.7%). The clinical presentation was similar to that described in the literature: young men with multifocal disease involving the trunk, face, mucosal and visceral involvement; and a good response to antiviral treatment and liposomal doxorubicin (9). An important feature, which has been described in the literature, is the occurrence of a few cases of KS despite a relatively high CD4 count (33). Furthermore, in 4 of the 30 patients in the current study, epidemic KS...
was diagnosed simultaneously with HIV infection. Specific features of epidemic KS, such as sexual intercourse between men (p=0.0054), should particularly raise the suspicion of HIV infection. Concerning the management and outcome of KS, a higher response rate was observed in patients with endemic KS compared with epidemic KS, as has already been reported in the literature (23).

Concerning the peaking incidence of endemic KS in the 1980s, it probably reflects the opening of a new dermatology unit in the 1980s, which allowed the diagnosis of many cases of endemic KS that had been evolving since the 1970s. In these cases, 5 patients were from Saint Lucia. The decrease in artisanal gold mining among Saint Lucians at the end of the 1990s may be associated with the decline in incidence rate of endemic KS. Brazilian immigrants have since replaced the Saint Lucians of Creole origin in mining jobs, and seem to be less affected by KS, as only one Brazilian patient was reported in our study.

The small proportion of Maroon (1/52, 1.9%) and Amerindian (1/52, 1.9%) is striking. As the overall Amerindian population does not exceed 10,000 inhabitants in French Guiana, it seems unsurprising that only 1 case of KS is recorded in this community. However, more cases could be expected, as a seroprevalence of 11.8–13.2% for HHV8 was found among Maroon people (5, 6) and 23% among groups of Amerindians (8) in previous studies. Seroprevalence was higher in Amerindians living in remote localities than in the coastal region (7). This high HHV-8 seroprevalence is probably caused by isolation and high rates of intrafamilial transmission in a general context of a low socioeconomic level and a traditional way of life. The low incidence of KS should not be linked to under-diagnosis, as these communities live in small villages where doctors and nurses of local health centres are very close to the inhabitants, and skin diseases rarely remain unnoticed. Therefore, the findings of the current study suggest that HHV8 seroprevalence does not always match the prevalence of KS.

Among the different clinical presentations reported in this study, we describe 1 striking case of anaplastic KS in an Amerindian patient. The anaplastic variant of KS was first described by Cox & Helwig (32) as a tumour exhibiting increased mitosis and severe cellular pleomorphism. The factors favouring this progression are not clearly understood, but duration of KS, chronic lymphoedema, a high number of treatments received, immunosuppression and viral coinfection with HIV have been implicated (34). In histopathological terms, anaplastic KS presents dense masses of relatively undifferentiated epithelioid cells, of medium-to-large size, with a high mitotic count and areas of necrosis. Expression of HHV8 antigen, CD34 and D240, along with the absence of epithelial markers and c-myc, will help pathologists to rule out epithelioid angiosarcoma (34). To the best of our knowledge, we report here the first case of anaplastic KS in South America. This rare, but severe, disease might be under-diagnosed in other Amerindian populations of the subcontinent. Recently, a fifth type of KS, KS affecting MSM without HIV infection, has been suggested (35). In the current study all MSM were infected with HIV, so we cannot conclude whether this form of KS exists in French Guiana.

This study has several limitations due to its retrospective and monocentric nature. However, the Andrée-Rosemon Hospital is the referral centre for KS for all French Guiana and patients from the remote areas are referred to the Dermatology Department for follow-up. Therefore, this study provides a good insight into the characteristics of KS in the general population of French Guiana.

This study reports a 50-year experience in the management of KS in a territory characterized by diverse ethnicities. While Creole populations seem to be as affected by endemic KS as their African counterparts, the dynamics of new cases of KS in French Guiana are now dominated by the epidemic form. Dermatologists should be familiar with these clinical signs, as they often represent a hallmark of HIV infection. The current study suggests specific clinical presentations of KS in Amerindians, which deserves further research. Specific host factors in Amerindians and Maroon people should be studied to explain the difference between a high HHV8 seroprevalence and a comparatively low prevalence of KS.

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The authors have no conflicts of interest to declare.

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