Int. J. Cancer: **65,** 200–203 (1996)

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

KAPOSI'S SARCOMA IN CHILDHOOD: AN ANALYSIS OF 100 CASES FROM UGANDA AND RELATIONSHIP TO HIV INFECTION

John L. ZIEGLER and Edward KATONGOLE-MBIDDE[1]
Uganda Cancer Institute, Kampala, Uganda.

We report 100 cases of Kaposi's sarcoma (KS) in children under 15 years of age treated at the Uganda Cancer Institute in the 6-year period 1989–1994. The incidence of childhood KS has risen more than 40-fold in the era of AIDS, and 78% of 63 cases tested were seropositive for HIV-1. There were 63 boys and 37 girls. The median age was 4 years and the median age of onset was 33 months. Tumour distribution was lymphadenopathic and muco-cutaneous, with 2 major patterns: pattern I, oro-facial dominant (79%); and pattern II, inguinal-genital dominant (13%). A newly described herpes-like virus is implicated as the cause of KS (KSHV), and DNA sequences of this virus were present in all of 8 childhood cases tested. If KSHV is a direct cause of KS, this tumour distribution in children suggests mucosal routes of virus entry, possibly during birth or breast feeding. The dramatic increase of childhood KS implies that the prevalence of causative factors is rising in Uganda.

Kaposi's sarcoma (KS) is now epidemic in countries where HIV is most prevalent. In Kyadondo County, Uganda (a peri-urban region that contains the majority of Kampala hospital referrals), KS accounts for half of the malignancies reported to the Kampala Cancer Registry in 1989–1991 (Wabinga *et al.,* 1993). KS comprises about 5% of AIDS-defining diagnoses, and has an estimated prevalence of 7 to 10% among HIV-infected patients (AIDS Control Programme, 1992; Desmond-Hellman *et al.,* 1991).

Prior to the HIV epidemic, KS was already endemic in Uganda, most common in older men from the western part of the country. Childhood KS was rare. Data from the Kampala Cancer Registry showed no cases recorded in 1954–1960 (Davies *et al.,* 1965) and in 1964–1968 just 2 cases in boys, a crude incidence of 0.3 per 100,000 (Taylor *et al.,* 1973). At the Uganda Cancer Institute, a major referral centre, only 12 cases were seen in 1968–1974 (Olweny *et al.,* 1976). Children had lymphadenopathic KS and an aggressive clinical course. With the advent of AIDS, childhood KS has become more common, both in the West (Gutierrez-Ortega *et al.,* 1989; Beral *et al.,* 1990) and in Africa (Bouquety *et al.,* 1989; Athale *et al.,* 1995).

Epidemologic evidence in Europe and North America implicates a sexually transmissible agent in the aetiology of AIDS-associated KS (Beral *et al.,* 1990). A herpes-like virus, discovered in KS tissues by molecular probe, has emerged as a potential causative agent, although the virus has not yet been isolated from KS tissues (Chang *et al.,* 1994). The best explanatory model posits the existence of an infectious KS agent that is sexually or enterally transmitted, has a long latency, and becomes expressed in circumstances of immune dysfunction (Peterman *et al.,* 1993). Biologic studies support a promotional role of paracrine cytokines, particularly the HIV Tat protein, that incite angiogenesis (Ensoli *et al.,* 1994).

If KS is caused by a transmissible agent, study of childhood KS may reveal clues of maternal passage of a KS agent, as infants and children are unlikely to acquire HIV by the sexual route. We report a retrospective analysis of 100 cases of KS in Ugandan children in the 6-year period 1989–1994.

PATIENTS AND METHODS

We reviewed the medical records of all children under 15 years of age with KS admitted to the Uganda Cancer Institute in the 6-year period between January 1989 and December 1994. During this period, facilities became available to assay HIV antibody using the Cambridge ELISA test and Western-blot confirmation (Desmond-Hellman *et al.,* 1991). Selected clinical and demographic data were abstracted and entered into EPIINFO 5.0 software for analysis. Statistical methods were those for descriptive studies with dichotomous variables including Chi-squared (2-sided with Yates correction) and Fisher's exact test. Incidence rates for Kyadondo County, the area covered by the Kampala Cancer Registry (Wabinga *et al.,* 1993), were calculated using the 1991 national census (Population and Housing Census, 1991). For comparison purposes, the rates from the earlier period (1964–1968; Taylor *et al.,* 1973) were age-standardized to the same population.

RESULTS

Histology

Exactly 100 cases were diagnosed in the 6-year period 1989–1994, 96 of which were confirmed histologically. The remaining 4 were diagnosed clinically by the appearance of characteristic skin or mucosal lesions and lymphadenopathy.

Age and sex

There were 63 boys and 37 girls in the case series, giving an overall male:female ratio of 1.7:1. The median age was 4 years. Figure 1 shows a histogram of the relationship between age and sex.

Associated lymphoma

Three children also had non-Hodgkin's lymphoma. One, a 10-year-old girl, had Burkitt's lymphoma and KS noted in the same mandibular tumour biopsy and Burkitt's lymphoma involving the clitoris. Another girl aged 3 had KS in soft-tissue nodules and Burkitt's lymphoma detected by aspiration cytology in a maxillary tumour. A 4-year-old boy had generalized lymphadenopathy and KS lesions; the skin tumours were KS and the lymph nodes showed lymphocytic lymphoma.

Incidence

Figure 2 shows the changing incidence of childhood KS in Kyadondo County. Using the 1991 census as defining the population at risk, incidence in the 0–14 year age in a 28-month period in 1989–1991 was 4.5 for boys and 2.7 for girls (Wabinga *et al.,* 1993). In 1992–93 these rates rose to 10.1 and 5.9 respectively. Compared with rates in the pre-AIDS era, these figures approximate to a 40-fold increase in incidence.

Family history

Details of birth circumstances, breast feeding, developmental milestones and early childhood history varied in the medical records, but there were no consistent features that

[1]To whom correspondence and reprint requests should be sent, at Uganda Cancer Institute, P.O. Box 3935, Kampala, Uganda. Fax: 256–41–221–895.

Received: May 29, 1995 and in revised form September 11, 1995.

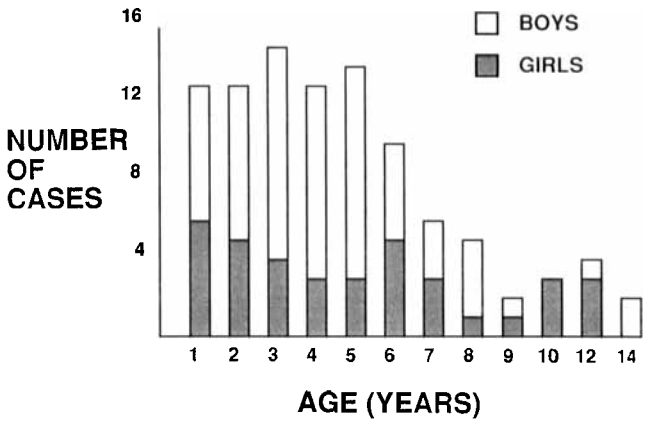

FIGURE 1 – Age and sex distribution in 100 children with Kaposi's sarcoma.

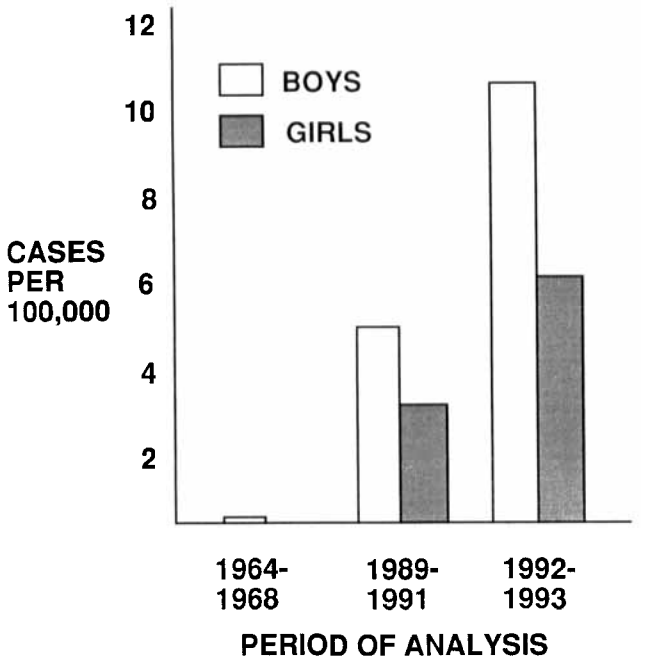

FIGURE 2 – Incidence rates of Kaposi's sarcoma in the childhood age range (0–14) in Kampala (Kyadondo County) Uganda in 3 time periods. The rates for 1964–1968 have been calculated from Taylor *et al.* (1972) and age-standardized to the 1991 population.

characterized the cases. The median birth order was 2 (range 1–9) and the median number of siblings was 3 (range 1–15). Illness in siblings was noted in 31%. Death or illness of mothers was present in 30% and of fathers in 20%.

There were 2 siblings, aged 3 and 6, who presented together in September, 1991. The older boy, while under treatment for tuberculosis, developed inguinal adenopathy and thigh nodules over a 6-month period. The younger brother then developed in one month generalized scalp and skin nodules after a long history of pyoderma. Both brothers were HIV-positive, as was their mother. The father died of an AIDS-like illness, but neither parent was known to have KS. There were 3 other cases in which siblings were reported to have died of similar conditions, and one whose father had a KS-like illness, but none of these reports could be confirmed.

Symptoms of HIV infection

A majority of patients (82%) gave a history of long-standing prodromal illness suggestive of HIV infection for a median of 7 months (range 2–60). Table I lists the main complaints. Noteworthy is the large number of children under treatment for suspected tuberculosis (37), diagnosed clinically because of cervical lymphadenopathy and respiratory symptoms.

Kaposi's sarcoma

KS lesions first noted by parents or by patients predominated in the head and neck (82%). The next most common sites were the extremities (7%), the inguinal region (5%) and intra-abdominal masses (4%). The median duration of KS lesions prior to presentation was 4 months (range 1–48). Thirty-nine patients described preceding infections (*e.g.*, pyoderma, oral sores, otitis, folliculitis) in sites that later became involved in KS.

On physical examination, the most prominent findings were regional or generalized lymphadenopathy, which was the sole physical finding in 14 children (Table II). Nodes involved were non-tender, firm, and mobile. Regional lymphoedema frequently accompanied adenopathy and was often severe and debilitating. Sites in the head and neck were the most frequently involved, followed by inguinal adenopathy and ano-genital KS lesions. Cutaneous lesions were present in 45 patients. These ranged from solitary nodules, often on the face and trunk, to widely disseminated plaques or nodules.

Although there was some overlap, 3 anatomic patterns of KS lesions could be discerned. Pattern I, seen in 79 patients, was dominated by KS lesions in the head and neck region, with regional (86%) or generalized lymphadenopathy (60%) and variable skin involvement (39%). Pattern II, observed in 13 patients, represented prominent KS lesions in the inguinal region, with inguinal lympadenopathy (100%), skin (57%) and ano-genital (14%) involvement. Pattern III, seen in 8%, was characterized by solitary tumours in the extremities or abdominal viscera.

Of 61 patients who had chest X-rays, 56 (92%) showed abnormalities, ranging from hilar adenopathy and mediastinal widening to diffuse pulmonary infiltrates with effusion. At least 11 patients had clinical involvement of abdominal viscera (mesenteric adenopathy, hepatic masses, colonic lesions, ascites) as detected by physical examination and ultrasonography. Due to limited facilities, visceral KS could not be diagnosed with certainty.

TABLE I – PRODROMAL SYMPTOMS PRECEDING KS IN 82 PATIENTS[1]

Head and neck	
Cervical lymphadenopathy	57
Thrush, oral sores	36
Otitis	10
Parotid swelling	8
Chest	
Cough (< 1 month)	58
Suspected tuberculosis	37
Pneumonia	7
Skin	
HIV rash	33
Pyoderma	23
Fungal infection	4
Herpes zoster	2
Molluscum contagiosum	2
Other symptoms	
Fever	76
Weight loss	70
Diarrhoea	38
Anaemia	35
Neurologic abnormality	4

[1]Some patients had multiple symptoms.

TABLE II – SITES OF KS ON PHYSICAL EXAMINATION IN 100 PATIENTS[1]

Lymphadenopathy	
Cervical	85
Inguinal	77
Axillary	70
Generalized	70
Head and neck	
Palate	18
Gingivae	13
Mandible/maxilla	9
Conjunctivae	9
Parotid	7
Tongue	6
Ear	2
Nose	2
Eyelid	1
Tonsil	1
Skin	45
Anogenital	15
Intra-abdominal (suspected)	11
Pulmonary (suspected)	5

[1]Some patients had involvement at more than one site.

TABLE III – RESULTS OF HIV-TESTING IN MOTHER-CHILD PAIRS

	Child with KS	
	HIV-positive	HIV-negative
Mother		
HIV-positive	21 (81%)	2
HIV-negative	5 (19%)	6
Total	26	8

Results of HIV testing

Sixty-three children and 35 mothers were tested for HIV antibody. Forty-nine children (78%) and 24 mothers (69%) were HIV-positive. The clinical features of HIV-positive and HIV-negative children did not differ. Of the 3 children with concomitant lymphoma, one was HIV-positive and 2 were negative.

Thirty-four mother-child pairs were tested for HIV. For 21 pairs, both were positive and for 6, both were negative (Table III). There were 7 discordant child-mother pairs. Five children were HIV-positive and their mothers HIV-negative. Three were known to have had prior blood transfusions, 2, 2 and 5 years before they became ill. All 5 had disseminated KS without features that might distinguish them from children who acquired HIV from their mothers. Two children were HIV-negative and their mothers HIV-positive. Both children, aged 2 and 4 years, were thought to have pulmonary tuberculosis, and both died within a year of presentation.

The age of onset can be estimated from the patient's age minus the individual duration of KS symptoms. In 21 HIV-positive child-mother pairs, this period was a median of 33 months (range 2–98), and in 6 HIV-negative child-mother pairs it was 34 months (range 11–108). The median age of onset for patients with unknown HIV status was 36 months.

Management and survival

Most patients were admitted at an advanced stage of illness. Twenty-three patients died within one month of admission, and 50 additional patients are known to have died. From the date of diagnosis, the median survival of patients who died was 3 months (range 1–42). Seventy patients were treated with a variety of chemotherapeutic regimens, and 12 patients (7 of whom are HIV-positive) have survived in clinical remission for 1 to 5 years.

DISCUSSION

The HIV epidemic in Uganda is now associated with epidemic KS in both adults and children. The rapidly rising incidence of childhood KS in the era of AIDS points to an increasing prevalence of causative factors in the environment. Of 63 children, 49 (78%) tested positive for HIV. For HIV-positive children whose mothers were also tested, 21 of 26 (81%) were also positive. Surprisingly, there were no child-mother pairs with KS, although the prevalence of KS in HIV-seropositive adults (7–10%) would predict about two mothers with KS. Two siblings presented together with KS, and suggestive evidence points to additional KS cases among other families.

Prodromal symptoms of HIV infection were present in the majority, and 39% of patients had an infection in a site later involved with KS. Over one-third of the children were under treatment for suspected pulmonary tuberculosis on admission. These findings suggest roles for immune dysfunction and local inflammation as predisposing factors in childhood KS. Further, KS lesions occassionally exhibit the "Koebner phenomenon" and appear in sites of previous trauma or infection (Neidt and Prioleau, 1989). This behaviour is reminiscent of Rous sarcoma, which appears in wounded areas of the chicken after infection with Rous sarcoma virus (Sieweke *et al.*, 1989), and supports a role for local growth factors in the pathogenesis of KS (Ensoli *et al.*, 1994).

Similar to "endemic" childhood KS (Olweny *et al.*, 1976), disease sites in this series predominate in mucous membranes and draining lymph nodes. The aggregation of sites in the head and neck (pattern I) or the inguinal and genital area (pattern II) favour the entry of a causative agent via oro-facial or anogenital mucosal routes. The median "incubation period" (*i.e.*, age of onset) of 33 months suggests that exposure to a potentially infectious agent could occur at birth or early infancy. The high concordancy of child-mother HIV seropositivity implies that the KS agent could spread to the child perinatally or during breast feeding.

The recent discovery of herpesvirus-like DNA sequences in KS tissues has raised the possibility of a long-sought aetiologic agent of KS (Chang *et al.*, 1994). The KSHV sequences have also been detected in 8 of 8 archival tissues taken from children in the current series (Chang *et al.*, 1995). If causative for KS, the agent must have been prevalent in Uganda prior to the AIDS era. The high rates of HIV infection may have amplified KSHV in the population, leading to the rising incidence of KS in adults and children.

ACKNOWLEDGEMENTS

Partial support for this study was provided by the Rockefeller Foundation and the University of California San Francisco AIDS Clinical Research Center. We thank Dr. C. Banura and Dr. F. Nakibirango who assisted in care of the patients, and Dr. M. MacGregor, who brought to our attention the 2 siblings with KS. Drs. K. DeCock, R. Newton, and V. Beral provided useful discussions, and Dr. D.M. Parkin assisted with the incidence calculations. We are also indebted to the Uganda Kaposi's Sarcoma Study Group. J.L.Z. is supported by the US Centers for Disease Control and Prevention and is a staff member of the International Agency for Research on Cancer, WHO.

REFERENCES

AIDS CONTROL PROGRAMME, HIV/AIDS Surveillance Report, Ministry of Health, Entebbe, Uganda (1992).

ATHALE, U.H., PATIL, P.S., CHINTU, C. and ELEM, B., Influence of HIV epidemic on the incidence of Kaposi's sarcoma in Zambian children. *J. acquir. Immun. Defic. Syndr. hum. Retroviruses,* **8,** 96–100 (1995).

BERAL, V., PETERMAN, T.A., BERKELMAN, R.L. and JAFFE, H.W., Kaposi's sarcoma among persons with AIDS: a sexually transmitted disease? *Lancet,* **335,** 123–128 (1990).

BOUQUETY, J.C., SIOPATHIS, M.R., RAVISSE, P.R., LAGARDE, N., GEORGES-COURBOT, M.C. and GEORGES, A.J., Lympho-cutaneous Kaposi's sarcoma in a African paediatric AIDS case. *Amer. J. Trop. Med. Hyg.,* **40,** 323–325 (1989).

CHANG, Y., CESARMAN, E., PESSIN, M.S., LEE, F., CULPEPPER, J., KNOWLES, D.M. and MOORE, P.S., Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science,* **266,** 1865–1869 (1994).

CHANG, Y., ZIEGLER, J.L., WABINGA, H., KATONGOLE-MBIDDE, E., BOSCHOFF, C., SCHULZ, T., WHITBY, D., MADDELENA, D., JAFFE, H.W., WEISS, R.A., UGANDA KAPOSI'S SARCOMA STUDY GROUP and MOORE, P.S., Kaposi's-sarcoma-associated herpesvirus DNA sequences are present in African endemic and AIDS-related Kaposi's sarcoma. *Arch. int. Med.* (1995). (In press).

DAVIES, J.N.P., KNOWELDEN, J. and WILSON, B.A., Incidence rates of cancer in Kyadondo county, Uganda, 1954–60. *J. nat. Cancer Inst.,* **35,** 789–821 (1965).

DESMOND-HELLMAN, S., MBIDDE, E.K., KIZITO, A., HELLMAN, N. and ZIEGLER, J.L., The value of a clinical definition for endemic Kaposi's sarcoma in predicting HIV seropositivity in Africa. *J. AIDS,* **4,** 647–651 (1991).

ENSOLI, B., GENDELMAN, R., MARKHAM P., FIORELLI, V., COLOMBINI, S., RAFFELD, M., CAFERO, A., CHANG, H-K., BRADY, J.N. and GALLO, R.C., Synergy between basic fibroblast growth factor and HIV-1 Tat protein in induction of Kaposi's sarcoma. *Nature (Lond.),* **371,** 674–680 (1994).

GUTIERREZ-ORTEGA, P., HIERRO-OROCZSO, S., SANCHEZ-CISNEROS, R., COYAOCAN, A. and NONTANO, L.F., Kaposi's sarcoma in a six-day-old infant with human immunodeficiency virus. *Arch. Dermatol.,* **125,** 4323 (1989).

NEIDT, G.W. and PRIOLEAU, P.G., Kaposi's sarcoma occurring in a dermatome previously involved by Herpes zoster. *J. Amer. Acad. Derm.,* **18,** 448–451 (1989).

OLWENY, C.L.M., KADDUMUKASA, A., ATINE, O., OWOR, R., MAGRATH, I.T. and ZIEGLER, J.L., Childhood Kaposi's sarcoma in Uganda: clinical features and treatment. *Brit. J. Cancer,* **33,** 555–560 (1976).

PETERMAN, T.A., BERAL, V. and JAFFE, H.W., Epidemiologic clues to the etiology of Kaposi's sarcoma. *AIDS,* **7,** 605–611 (1993).

POPULATION AND HOUSING CENSUS, 1991, *Kampala District.* Statistics Department, Ministry of Finance and Economic Planning, Entebbe, Uganda (1992).

SIEWEKE, H., STOKER, A.W. and BISSEL, M.J., Evaluation of the co-carcinogenic effect of wounding in Rous-sarcoma-virus tumorigenesis. *Cancer Res.,* **49,** 6419–6424 (1989).

TAYLOR, J.F., SMITH, P.G., BULL, D. and PIKE, M.C., Kaposi's sarcoma in Uganda: geography and ethnic distribution. *Brit. J. Cancer,* **26,** 483–595 (1973).

WABINGA, H.R., PARKIN, D.M., WABWIRE-MANGEN, F. and MUGERWA, J.W., Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. *Int. J. Cancer,* **54,** 26–36 (1993).