Penile Kaposi's sarcoma in the state of California

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Introduction: *Penile Kaposi's sarcoma (PKS) is a rare and poorly characterized disease. Kaposi's sarcoma is common in HIV disease and is an AIDS-defining illness. This study aimed to review epidemiologic characteristics and changes in the incidence of PKS using a total population-based database.*
Materials and methods: *Data from the California Cancer Registry (CCR) were reviewed for the years 1988-2004, identifying all cases of penile cancer. Tumors were classified by histology and stage. Annual age-adjusted incidence and actuarial survival rates were calculated for the overall population and subdivided histology.*
Results: *From 1988-2004, 2870 cases of penile cancer were identified. Squamous cell carcinoma accounted for 87% of all penile cancer (n = 2507), and PKS was the second most common, accounting for 4.6% (n = 132). Patients diagnosed with PKS demonstrated a significantly lower mean age (years) than the overall cohort (43.7 versus 62.6, p < .0001). The incidence of PKS peaked in 1992 with a subsequent dramatic decline, the same year as incident AIDS cases. The percentage of all penile cancer comprised by PKS dropped from 7.4% in the 1988-1995 cohort to 1.7% in the 1995-2004 cohort (p < 0.0001). Patients diagnosed with PKS demonstrated a significantly lower 5 (32.8% versus 76.6%, p < .0001) and 10 year (29.5% versus 69.6%, p < .0001) relative overall survival than those with squamous cell carcinoma.*
Conclusion: *PKS is the second most frequent malignancy of the penis, occurring at a younger age and portending a worse prognosis than other forms of penile cancer. The proportion of PKS tumors has declined in recent years, reflecting improvements in HIV treatment that occurred during the study period.*

Key Words: Kaposi's sarcoma, penile cancer, HIV, incidence, California Cancer Registry

Introduction

While the natural history and treatment of squamous cell carcinoma (SCC) of the penis is relatively well understood,[1] there is a paucity of systematic data on rarer penile tumor histologies. We performed an exploratory analysis of all tumors of the penis reported to the California Cancer Registry (CCR) between 1988 and 2004. The CCR is a mandatory cancer registry accruing all cases of malignancy in the state of California except non-melanomatous skin cancers since 1988 with state enforced penalties for failure to report cases. In subsequent years, CIS of the uterine cervix and "borderline" tumors of the ovary have also been excluded. The CCR includes over 2.5 million incident cancer diagnoses with over 140,000 cases registered annually, and in 2001, the entire state became a part of Surveillance, Epidemiology and End Results (SEER).[2]

Kaposi's sarcoma is a rare tumor that can affect multiple organ systems, including the penis. While isolated involvement of the penis is rare,[3] it has varied and subtle clinical presentations that can make it difficult to diagnose.[4] Furthermore, little is known about the natural history of penile Kaposi's sarcoma as compared to other cutaneous forms of the disease. To our knowledge, there have been no population-based studies examining this condition. We compared epidemiologic characteristics, overall survival and changes in incidence between penile Kaposi's sarcoma (PKS) and SCC over the 17 year study period.

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Materials and methods

We identified all cases of penile cancer in the CCR from the years 1988-2004, searching by tumor location. Tumors were classified by histologic subtype and stage. We compared mean age by tumor histology. Census data were obtained from the U.S Census bureau[5] and used to provide a rough estimate of PKS incidence. Annual case totals were compared to evaluate trends in PKS incidence over the course of the study. Actuarial mortality rates were calculated by subdivided histology. Data on the incidence of HIV and AIDS were obtained from the California Department of Public Health, which began confidential AIDS case reporting in 1983.[6] Data on annual mortality in AIDS patients were obtained from the Center for Disease Control, which has monitored AIDS incidence since 1981.[7]

Statistical analyses were completed using Z-tests for continuous variables, chi-squared analyses for categorical variables and the Berkson-Gage life table method[8] for calculating overall relative survival. Incidence was calculated by dividing the mean cases of PKS over the study period by the mean population of males in the state of California using data from the 1990 and 2000 US censuses.[5,9] Relative survival rates compare the mortality of a cohort of patients to a similar group from the general population thus measuring the impact of the disease on survival regardless of cause of death. Statistical significance was set at $p < 0.05$.

Results

We identified 2870 cases of penile cancer between 1988 and 2004. Squamous cell carcinoma (SCC) accounted for 87% of all penile cancer (n = 2507), and PKS was the second most common variant, accounting for 4.6% (n = 132). Sarcoma not otherwise specified represented < 1% (n = 14). Patients diagnosed with PKS were significantly younger with a mean age of 43.7 years, compared with the overall cohort at 62.6 years ($p < 0.0001$) Table 1.

The incidence of PKS peaked in 1992 at 22 cases with a subsequent dramatic decline, Figure 1. As evidence of this decrement, the percentage of all penile cancers comprised by PKS dropped from 7.4% in the 1988-1995 cohort to 1.7% in the 1995-2004 cohort ($p < 0.0001$). The incidence of AIDS in the state of California also peaked in 1992 at 12,234 cases with a subsequent dramatic decline, Figure 1.[6] To protect patient confidentiality, the CCR requires that individual data points with five or fewer cases be presented as ≤ 5. Therefore, we have divided the most recent years into 4 year average as demonstrated in Figure 1. There were a total of 25 incident cases between 1997 and 2004, and each of these years had less than or equal to five incident cases.

There were a total of 14,897,627 men living in the state of California during the 1990 census.[5] Another census occurred during the course of our study in 2000 at which time the male population had risen to 16,874,892.[9] Using the mean cases of PKS over our study

TABLE 1. **Penile tumor histology and age**

Tumor type	Number of patients	Percent of all cases	Mean age at presentation (years)
Squamous cell carcinoma	2507	87.4%	63.6
Kaposi's sarcoma	132	4.60%	43.7
Cancer NOS	119	4.15%	58.8
Adenocarcinoma	41	1.43%	69.5
Melanoma	23	0.80%	3.1
Basal cell carcinoma	21	0.73%	67.8
Sarcoma NOS	14	0.49%	43.7
Transitional cell carcinoma	13	0.45%	71.5
Total	**2870**	**100%**	**62.6**

period and the mean population, the incidence of PKS is estimated at 4.88 cases per 10 million men per year.

Patients diagnosed with PKS demonstrated a significantly lower 5 (32.8% versus 76.6%, p < .0001) and 10-year (29.5% versus 69.6%, p < .0001) relative overall survival than those with SCC, Figure 2. There were not sufficient cases of PKS to compare 5 year survival rates between 1988-1995 and 1995-2004 PKS cohorts. Figure 3 demonstrates the marked improvement in survival among HIV positive patients nationally beginning in the mid 1990's.

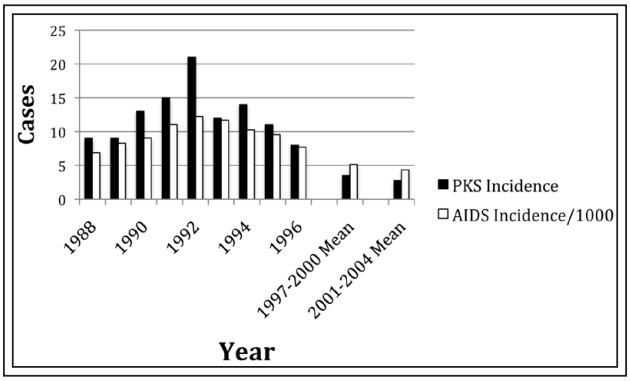

Figure 1. Incident cases of PKS and AIDS[6] by year.

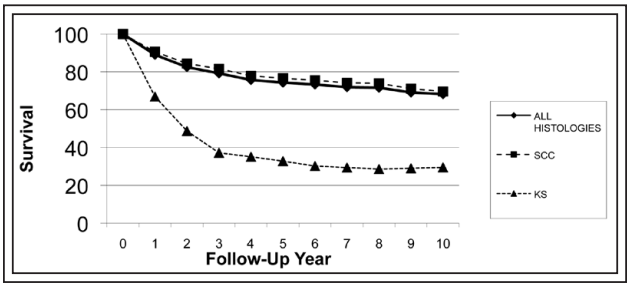

Figure 2. Overall relative survival by penile cancer histology.

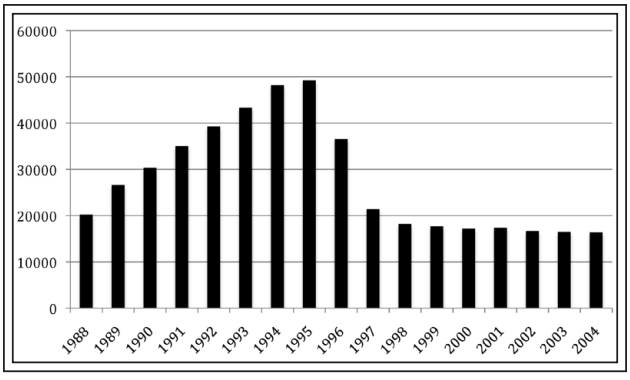

Figure 3. Annual mortality data in AIDS patients.[7]

Discussion

Ours is the largest and first population-based study to our knowledge investigating the behavior of Kaposi's sarcoma (KS) of the penis, a rare and previously poorly characterized condition. These data suggest that PKS behaves differently from other forms of penile cancer, occurring in younger men and portending a graver prognosis. Previously published data suggest that isolated involvement of the penis occurs in less than 3% of patients with KS, however 20% of KS patients progress to develop genital involvement.[3] Lesions may be dull, scaled or ulcerating reddish-brown to violaceous macules, plaques or nodules sometimes preceded by lymphedema.[4] While treatment of KS is rarely surgical, this variable appearance may require biopsy for tissue diagnosis. Uncommonly, urologic surgical intervention is necessary because of tissue loss or urethral obstruction.[10,11]

KS affects four distinct populations worldwide.[12] The classic form is indolent occurring in middle-aged men of Mediterranean descent. The endemic form is somewhat more aggressive, occurring in regions of Africa such as Uganda and Zambia. Immunosuppressive KS is a rare complication of anti-rejection medication in organ transplant recipients. It is the epidemiology of the fourth group, however, that likely accounts for most of the differences between PKS and other forms of penile cancer. The largest cohort of KS in American series since the late 1980's occurs in the setting of HIV disease.[13] Although the HIV status of patients is not captured in the CCR, the similarities between the epidemiology of AIDS and PKS are compelling, Figure 1. There are also molecular biologic data to suggest a prominent role of HIV in the pathogenesis of KS.[14,15]

Human herpes virus-8 infection is necessary for the development of Kaposi's sarcoma in all four forms, but is generally insufficient on its own for the development of clinical disease.[12] HIV coinfection, while not necessary for the development of KS, potentiates the risk for malignant cellular transformation. Depletion of CD4+ T-cells exhausts the oncologic policing function of the immune system in determining self from non-self. Increased levels of certain cytokines, such as TNF-alpha and IL-6, resulting from opportunistic infections and HIV disease progression stimulate KS proliferation.[15] An HIV-derived protein, TaT, also directly stimulates KS cell growth.[14]

Although it is decreasing in incidence, KS remains the most frequent AIDS-associated cancer and is an AIDS-defining illness.[16-19] The relative risk for KS in an HIV infected individual is estimated at 1300 times that of the general population and remains

substantially elevated even in the highly active antiretroviral therapy (HAART) era.[19] KS demonstrates an inverse relationship to CD4 count but can develop at any level.[20-22] HIV disease occurs in a much younger population than SCC of the penis, which was apparent in the younger age of the PKS cohort in our study, Table 1. Hall et al reviewed epidemiologic characteristics of incident HIV infections in 22 US states in 2006 and found that 66% of patients were younger than 40 and only 11% older than 50.[23] Because KS is more common in patients with advanced and poorly controlled HIV disease, it may explain the poorer survival in the PKS group as well, Table 1. For example, in 1994, less than 50% of patients diagnosed with AIDS on the basis of an opportunistic illness such as KS, were alive at 24 months.[24] National mortality rates in patients diagnosed with AIDS more than doubled from 1988-1995 and then dropped substantially thereafter, Figure 3.[7] These data suggest that the survival rate of PKS demonstrated in our study, Figure 2, is similar to that of cutaneous KS in other regions of the body.[25]

The first combined antiretroviral regimen emerged in 1991, and the first protease inhibitor in 1995.[26] These seminal events in HIV therapy echo decrements in the incidence of PKS, Figure 1, and the mortality of AIDS, Figure 3, occurring over the time course of our study. The development of HAART has impacted HIV progression enormously, as demonstrated by decreased viral loads, stabilized CD4 counts and decreased incidence of opportunistic diseases.[19] Life expectancy in patients with well-controlled HIV on HAART approaches that of the general population.[27] HAART impacts the incidence and prognosis of KS indirectly by allowing for immune reconstitution and directly by suppressing viremia and thus TaT levels. Multiple studies have demonstrated a decreased incidence of KS since the development of HAART.[16-18,21] A recent comparison of HIV seroconverters in the HAART and pre-HAART eras demonstrated equal efficacy of the combined regimen in decreasing the risk of cancer and non-cancer AIDS-defining events. Seventy-nine percent of the cancer events in this study were KS.[28] Use of HAART has a more marked effect on decreasing the incidence of visceral KS, an entity associated with a worse prognosis than cutaneous KS.[29] Survival in patients with pulmonary KS, the most lethal form, improved with administration of HAART in addition to chemotherapy as compared to chemotherapy alone.[30] The significant decrease in the proportion of penile cancer represented by Kaposi's Sarcoma between 1988-1995 and 1996-2004 reflects the changing epidemiology of HIV disease in the HAART era, Figure 1. A change in survival rate could not be concluded in this study since the majority of incident cases occurred prior to 1995.

Other factors could have played a role in the apparent decline in PKS incidence observed in our study, including a potential reporting bias on the basis of tumor location. While there are cases of penile cancer captured without a tissue diagnosis, over 98% of cases in the CCR provide histologic confirmation. The primary treatment modalities for Kaposi's sarcoma are non-surgical using radiation and/or chemotherapy as well as immune reconstitution.[12] Complications of PKS requiring surgical intervention that might lead to a tissue sample are rare. Furthermore, Kaposi's sarcoma is usually multifocal, and patients typically have an unequivocal diagnosis by the time they develop penile lesions. Since our data were generated primarily from tissue diagnoses, increased clinical recognition of characteristic lesions with improving familiarity with HIV over time or biopsy from alternative sites may have decreased the number of true cases accrued in the CCR as our study progressed. Nonetheless, our data parallels overall trends in Kaposi's sarcoma incidence generally, and our study represents the first published incidence of PKS from a population-based study.[16-18,21] These same limitations of reporting bias and incomplete patient accrual potentially affect the accuracy of our estimated annual incidence rate of the disease. Since our study seems to have captured the disease in the course of evolution, caution should also be exercised in extrapolating these incidence rates to the modern era. The financial penalty imposed by the CCR for failure to disclose cases should limit inaccuracy from underreporting and represents a strength of this database as compared to other population-based cancer registries. Additional limitations include the lack of additional demographic and clinical data including race, HIV status, medical comorbidity and treatment inherent to the limited scope of the CCR database. Since California was an epicenter of HIV disease, the incidence of PKS demonstrated in our study may not be reflected in other regions with a lower prevalence of HIV.

Conclusion

Kaposi's sarcoma of the penis is the second most common form of penile cancer. It is decreasing in incidence, affects younger men and has a worse 5 and 10 year survival than SCC of the penis. It is likely that improvements in the management of HIV disease that occurred over the course of this study dramatically impacted the epidemiology and prognosis of this condition.

Disclaimer

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EDITORIAL COMMENT

This is a very interesting paper showing the changes in prognosis of HIV/AIDS and penile Kaposi's sarcoma (PKS) in the state of California. The 17 year period of the study witnessed the changes in HIV prevention, incidence, treatment and prognosis. Physicians in California were at the forefront of HIV identification and research. The falling incidence of PKS may be due to lower AIDS incidence, however inspection of Figure 1 would appear to show that the ratio of PKS to AIDS dropped from 1997 onwards, which suggests that the natural history of AIDS progressing to PKS has been modified. The authors are careful to point out the potential limitations of reporting of PKS, however compulsory registration of cases in the state improve the veracity of the data. The reduced incidence in the latter years means it is as yet not possible to see if overall survival is also improved in those diagnosed with PKS. These data should be of interest to all physicians not just urologists.

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