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Epidemiologic Profile, Sexual History, Pathologic Features, and Human Papillomavirus Status of 103 Patients with Penile Carcinoma

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Abstract

PURPOSE—The incidence of penile cancer is four times higher in Paraguay than in the United States or Europe. There are no adequate scientific explanations for this geographical variation. The goal of this study was to evaluate the interplay among risk factors, morphology of the primary tumor, and HPV status.

METHODS—Information on socioeconomic status, education level, habits, and sexual history was obtained in 103 Paraguayan patients with penile cancer. All patients were then treated by surgery and specimens were evaluated histopathologically.

RESULTS—Patients usually dwelled in rural/suburban areas (82%), lived in poverty (75%), had a low education level (91%), and were heavy smokers (76%). Phimosis (57%), moderate/poor hygienic habits (90%), and history of sexually-transmitted diseases (74%) were frequently found. Patients with >10 lifetime female partners had an odds ratio of 3.8 (95% CI 1.1, 12.6; *P*-trend = .03) for presenting HPV positive tumors when compared to patients with <6 partners. However, this trend was not significant when the number of sexual partners was adjusted for age of first coitus and antecedents of sexually-transmitted diseases. HPV-related tumors (found in 36% of the samples) were characterized by a warty and/or basaloid morphology and high histological grade in most cases.

CONCLUSIONS—In our series, patients with penile cancer presented a distinctive epidemiological and pathological profile. These data might help explaining the geographical differences in incidence and aid in the design of strategies for cancer control in Paraguay.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

Keywords

penile cancer; human papillomavirus; circumcision; phimosis; lichen sclerosus; risk factors

INTRODUCTION

Penile cancer is rare in most developed areas of the world. However, the age-standardized incidence rate per 100,000 inhabitants (ASR) is widely variable depending on the geographical region under consideration. In North America and Europe it ranges from 0.1–1.0 while certain African and South American countries show a two or three-fold increased incidence [1,2]. In this regard, the ASR of penile carcinoma in Paraguay is among the highest worldwide, with a reported value of 4.2, according to last available data from the International Agency for Research on Cancer (IARC) [2]. There are no adequate scientific explanations for this geographical variation but known risk factors, such as lack of circumcision, phimosis, smoking, a history of penile tears, chronic inflammatory conditions, poor genital hygiene, and the presence of human papillomavirus (HPV) infection [3], might be more prevalent in areas with a higher incidence.

Similarly to vulvar and head and neck carcinomas [5,6], penile cancer seems to follow a bimodal pathogenic pathway, one associated with and the other unrelated to HPV infection [7,8]. Unlike uterine cervical cancers, in which most tumors are HPV-related, only 30–50% of penile cancers show evidence of HPV infection [4,8,9]. The association between HPV and histological subtype of penile squamous cell carcinoma (SCC) has been evaluated [10] but we found no prospective studies assessing these and other pathologic features taking also into account demographics and clinical data, including life-style habits and sexual history. The main objective of this study was to evaluate the interplay among known epidemiological risk factors, morphologic features of the primary tumor, and HPV status in a prospective cohort of penile cancer patients from Paraguay.

MATERIAL AND METHODS

An *ad hoc* Institutional Review Board at the School of Medicine, Universidad Nacional de Asunción (Asunción, Paraguay) approved the study protocol, in accordance with the ethical standards of the 1964 Declaration of Helsinki. Informed consent was obtained from all patients.

Case Selection and Data Acquisition

Between 1993 and 2007, a questionnaire was prospectively administered to 103 Paraguayan patients with penile cancer. Cases were originally diagnosed and treated in Paraguayan clinics and hospitals from the public sector. Senior medical students and pathology residents conducted the interviews before implementation of any form of treatment. Foreskin length was determined following previously published criteria [11]. Hygienic habits were determined by combining data on frequency of genital washes (daily washes, nondaily washes but more than 1 wash per week, and less than 1 wash per week) and self-reported presence of smegma (almost never, sometimes, and frequent). All patients were treated by either partial/total penectomy or circumcision. Bilateral inguinal lymphadenectomy was performed in 25 patients at the time of or within 30 days from primary surgery for clinically-apparent nodal involvement.

Pathologic Evaluation

Classification of preneoplastic lesions and invasive tumors was done according to the criteria proposed in the AFIP Atlas of Tumor Pathology [12]. The aforementioned criteria include the criteria used for the World Health Organization (WHO) classification of penile tumors, in addition to criteria for the diagnosis of recently-described pathologic entities. Histologic grading was carried out using previously published criteria [13].

Immunohistochemistry for p16^{INK4a} (CINtec®, MTM Laboratories AG, Heidelberg, Germany) was carried out in 88 patients. Tumor tissue for HPV detection and genotyping was available in 89 cases and it was done by SPF-10 polymerase chain reaction (PCR) and Li-PA₂₅ version 1 (Labo Biomedical Products, Rijswijk, the Netherlands), at the Institut Català d'Oncologia (Barcelona, Spain), following a previously described protocol [9].

Statistical Analysis

Variables were compared using the Fisher's exact or the Student's t-test. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using binary logistic regression. In all cases, a 2-tailed $P < 0.05$ was required for statistical significance. Data were analyzed using the software PASW version 18.0 (IBM Inc., Somers, NY).

RESULTS

Epidemiologic and Clinical Features

The majority of patients lived in rural or suburban regions and received only elementary education (6 years of school). The gross familial income was below the minimal wage in most cases. Socioeconomic data are summarized in Table 1, section A.

Mean age of patients was 62 years. Most patients reported past or present consumption of tobacco, mainly in the form of cigarettes, and 55% of them still held the habit. Long foreskins and phimosis were detected in about one half of all patients. Circumcision was done in a minority of patients for medical reasons, such as chronic inflammation or phimosis. Most patients reported moderate to poor genital hygienic habits. A previous history of STD was reported by 76% of patients. These and other data (including sexual history) are summarized in Table 1, section B.

Pathological Features

Pathological data are summarized in Table 1, section C. Most tumors were clinically advanced and located in the distal penis, affecting multiple epithelial compartments in more than one half of the cases. When limited to one anatomical compartment, glans was more frequently affected, followed by inner foreskin. Invasive carcinomas predominated over in situ lesions (98% vs. 2%). The predominant histologic subtype was usual SCC (32%), followed by mixed SCC (18%), basaloid carcinoma (12%), and papillary carcinoma (11%). Warty and warty-basaloid carcinomas were less frequently found (7% and 6%). Other subtypes included pseudohyperplastic (4%), verrucous (3%), sarcomatoid (3%), multicentric usual & verrucous (2%), cuniculatum (1%), and clear cell (1%) carcinomas. Inguinal nodal metastases were found in 18 patients (72% of all patients who received groin dissections). Differentiated PeIN was the most common preneoplastic lesion found, followed by PeIN with warty and/or basaloid features, and mixed PeIN. Lichen sclerosus was observed in about two-third of the cases. Overexpression of p16^{INK4a} in invasive carcinomas was observed in 24% of the cases. HPV DNA was detected in 36% of the analyzed tissue samples.

Epidemiological, Clinical, and Pathologic Features and HPV status

Epidemiologic, clinical, and pathological features of patients with penile cancer according to HPV status are presented in Table 2. No significant differences in socioeconomic features were noted. Among the clinical features, only the mean number of lifetime female sexual partners was different between these two groups, with a higher value in patients with HPV positive tumors.

HPV positive tumors tended to show warty and/or basaloid features, to correspond to a higher histological grade, and to be associated with subtypes of PeIN depicting similar morphological features as their invasive counterparts. HPV negative carcinomas were usually well to moderately differentiated tumors, frequently associated with differentiated PeIN and lichen sclerosus. Overexpression of p16^{INK4a} was more prevalent in HPV positive tumors (Figure 1). Anatomical location of the primary tumor was similar in both groups of patients. Metastatic ratios were not significantly different in HPV positive and HPV negative tumors (60% vs 79%, $P = .57$).

The comparison of epidemiologic and clinical risk factors of the patients according to HPV status disclosed similar features, except for the categorized number of lifetime sexual female partners (Table 3). The risk for HPV positive penile tumors was almost 4 times higher among patients with >10 lifetime female partners compared to individuals with <6 partners. However, this trend lost significance when the covariate was adjusted for age of first coitus and antecedents of STD (OR 1.75; 95% CI 0.96, 3.19; $P = .067$).

DISCUSSION

In this prospective study we are reporting the socioeconomic profile, presence of risk factors, sexual history, tumor morphologic features, and HPV status of patients with penile carcinomas. The epidemiological characteristics are those already described in other studies [14–16]. The majority of penile cancer patients in Paraguay were from rural or suburban areas. This represents a demographic change considering that, in a previous report from the 1960's, most patients lived in rural regions [17]. This shift might be related to a recent significant migration from rural to suburban areas. However, suburban people, unlike their counterparts in developed nations, live under harsh conditions and are culturally and socioeconomically underserved, similar to rural patients. In countries where 20% or more of the population live in poverty, such is the case in Paraguay, the risk for penile cancer is 43% higher than in countries with less than 10% poverty levels [16].

The majority of our patients (76%) were heavy smokers. There is a clear dose response relation of smoking with penile cancer. Previous studies have shown that patients smoking more than 10 cigarettes per day, as the majority of our patients, had a significantly higher risk than light smokers [14]. In a recent series, Koifman et al [18] also found a high incidence of smoking among Brazilian penile cancer patients (56.5%). Nevertheless, the exact mechanisms and precise role that smoking plays in penile cancer development is largely unknown.

The “foreskin factor” is important in penile cancer oncogenesis since there is strong evidence that circumcision at birth, as it is ritually practiced in the Jewish, Muslim, and other populations, prevents its occurrence [3]. Most of the Paraguayan patients in this study were uncircumcised. The few individuals reporting a history of previous circumcision (10%) had the procedure performed within the context of a symptomatic medical condition. Circumcision was also uncommon in Brazilian patients, according to Koifman et al [18]. Some studies suggest that circumcision practiced at adulthood, even in those cases done by religious or cultural reasons, instead of protecting against, is associated with an increased

risk of penile cancer, especially when extensive scarring develops [19]. A possible explanation for this seemingly contradictory phenomenon could be related to the development of the scar itself or to the presence of subclinical penile lesions at the time of the procedure.

The protective effect of newborn circumcision is probably linked to the prevention of phimosis [3]. In an early study, Hellberg et al reported a relative risk of 64.6 for penile cancer among men with phimosis [20]. Following this study, several others have confirmed the role of phimosis as a risk factor for tumor development [14,3]. The high prevalence of difficulty in retracting the foreskin we found (57%) is similar to the figures reported in Northeastern Brazil by Favorito et al [21]. A frequent association of phimosis with lichen sclerosus in our series (74%) suggests a causal link. Other interesting findings were those related to the sexual history of patients with penile cancer. As an unadjusted covariate, patients with a sexual history of > 10 lifetime female partners were more prone to present HPV positive tumors. A similar trend has been reported in women in regards to the risk of cervical carcinomas [22].

One possible limitation of the present study is the lack of an age-matched control group for patients with penile cancer. However, this study was designed to explore the association of pathologic features of penile tumors with clinical and epidemiologic features of the targeted population. We did not aim to identify or evaluate risk factors for the development of penile cancer in the general population. In this sense, we built upon previously recognized risk factors, such as smoking, foreskin features, circumcision status, and sexual history [3,14,12,20]. Studies with similar designs to our design are scant, especially from regions of high prevalence. Our results could help unravel the complex pathogenesis of penile cancer and contribute in the understanding of its differential distribution across different geographical regions.

In summary, we have described the epidemiological, clinical, and pathological profile of patients with penile SCC in Paraguay, a geographical region with one of the highest rates in penile cancer. Patients usually lived in rural/suburban areas, in poverty, and had a low education level. Most of them were heavy smokers. Circumcision was uncommon and, when practiced, was related to the presence of medical conditions. Long foreskins and moderate/poor genital hygienic habits were also frequently found, as well as a high reported history of sexually transmitted diseases. HPV-related tumors were characterized by a warty and/or basaloid morphology, high histological grade, and association with precursor lesions showing similar features to their invasive counterparts while HPV negative tumors were well to moderately differentiated SCC, frequently associated with lichen sclerosus and differentiated PeIN. These data might help in the development of strategies for penile cancer control in Paraguay.

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Figure 1. Morphological features of HPV-related penile tumors

HPV positive basaloid carcinoma (upper left, H&E) showing invasive tumors nests; neoplastic cells are strongly positive for p16^{INK4a} expression (upper right). Warty carcinoma (lower left, H&E) depicting papillae with prominent parakeratosis and conspicuous koilocytosis; p16^{INK4a} overexpression is observed in tumor cells but not in the parakeratotic layer (lower right).

TABLE 1

Socioeconomic, Clinical, and Pathologic Profile of 103 Patients with Penile Cancer

A) SOCIOECONOMIC FEATURES	No. cases (%)
Residence	
Urban	18 (17)
Suburban	44 (43)
Rural	41 (40)
Formal Education	
No Education	16 (15)
Primary Education	78 (76)
Secondary Education	7 (7)
Tertiary Education	2 (2)
Familial Income	
<1 Minimal Wage	77 (75)
1 Minimal Wages	26 (25)
B) CLINICAL FEATURES	
Age, median [range]	65 y [26–83 y]
Smoking Habits	
No. smokers	78 (76)
Age of onset [range]	19.6 y [7–36 y]
Years of Smoking [range]	30.9 y [1–66 y]
No. cigarettes/day [range]	10.4 [1–60]
Foreskin Features	
Long foreskin	48 (47)
History of Phimosis	59 (57)
Previous Circumcision	10 (10)
Age of Circumcision [range]	54.1 y [27–74 y]
Genital Hygiene	
Moderate/Poor	92 (89)
Good	11 (11)
History of STD	
	76 (74)
Sexual History	
Age of first coitus [range]	17.4 y [12–27 y]
Average of female partners [range]	13.3 [1–100]
No. female partners	
Less than 6	26 (25)
Between 6 and 10	17 (17)
More than 10	60 (58)
C) PATHOLOGICAL FEATURES	
Anatomical Site	
Glans	28 (32)

A) SOCIOECONOMIC FEATURES	No. cases (%)
Foreskin	10 (11)
Multiple compartments	50 (56)
Shaft skin	1 (1)
Histological Subtypes	
No warty/basaloid features	63 (62)
With warty/basaloid features	39 (38)
Histological Grade	
Grade 1	34 (34)
Grade 2	26 (26)
Grade 3	41 (40)
Penile intraepithelial neoplasia (N=70)	
Differentiated	45 (64)
Warty/basaloid features	15 (22)
Mixed	10 (14)
Lichen sclerosis (N=67)	45 (67)

TABLE 2

Socioeconomic, Clinical, and Pathological Features of Penile Cancer Patients by HPV Status

	HPV- (%) N=57 (64)	HPV+ (%) N=32 (36)	P-value
A) SOCIOECONOMIC FEATURES			
Residence			.83
Metropolitan	32 (56)	19 (59)	
Rural	25 (44)	13 (41)	
Formal Education			.42
No Education	6 (11)	7 (22)	
Primary Level	47 (82)	22 (61)	
Secondary Level	3 (5)	2 (6)	
Tertiary Level	1 (2)	1 (3)	
Familial Income			.30
<1 Minimal Wages	42 (74)	27 (84)	
1 Minimal Wages	15 (26)	5 (16)	
B) CLINICAL FEATURES			
Mean Age	60	65	.13
Smoking Habits			
Smoker	42 (74)	24 (75)	.99
Mean age of onset	20.4	18.4	.16
Mean years of smoking	30.3	33.5	.44
Mean No. cigarettes/day	8.5	12.8	.13
Years of Smoking			.96
Non-smoker	15 (26)	8 (25)	
Less than 30 years	23 (40)	12 (37.5)	
30 years or more	19 (33)	12 (37.5)	
Packs/Year of Smoking			.13
Non-smoker	15 (26)	8 (25)	
10 packs/year	25 (44)	8 (25)	
>10 packs/year	17 (30)	16 (50)	
Foreskin Features			
Presence of long foreskin	24 (42)	17 (53)	.38
Prior circumcision	3 (5)	6 (19)	.07
History of phimosis	36 (63)	16 (50)	.27
Genital Hygienic Habits			.99
Moderate/Poor Hygiene	51 (90)	29 (91)	
Good Hygiene	6 (10)	3 (9)	
Sexual History			
History of any STD	42 (74)	27 (84)	.30
Mean age of first coitus	17.7	16.7	.10
Mean No. female partners	10.5	16.1	.04

	HPV- (%) N=57 (64)	HPV+ (%) N=32 (36)	P-value
C) PATHOLOGICAL FEATURES			
Anatomical Site			.41
Glans	16 (32)	7 (26)	
Foreskin	5 (10)	1 (4)	
Multiple	29 (58)	18 (66)	
Penile Shaft	0 (0)	1 (4)	
Histological Subtypes			< .001
No warty/basaloid features	44 (77)	9 (29)	
With warty/basaloid features	13 (23)	23 (71)	
Histological Grade			.005
Grade 1	25 (44)	4 (12.5)	
Grade 2	12 (21)	8 (25)	
Grade 3	20 (35)	20 (62.5)	
Penile Intraepithelial Neoplasia			< .001
Differentiated PeIN	34 (78)	5 (28)	
Warty and/or basaloid PeIN	5 (11)	9 (50)	
Mixed PeIN	5 (11)	4 (22)	
Lichen sclerosis	32 (78)	7 (37)	.003
p16^{INK4a} overexpression	6 (11)	15 (48)	< .001

TABLE 3

Socio-Demographic, Sexual, and Behavioral Risk Factors for HPV-Related Penile Cancer, Compared to HPV Negative Cases

	Odds Ratio (95% CI)	P-trend value
Years of Smoking		.78
Non-smoker	1 ^a	
Less than 30 years	1 (0.3, 3)	
30 years or more	1.2 (0.4, 3.6)	
Packs/Year of Smoking		.26
Non-smoker	1 ^a	
10 packs/year	0.6 (0.2, 1.9)	
>10 packs/year	1.8 (0.6, 5.3)	
Genital Hygienic Habits		.32
Poor Hygiene	1.6 (0.3, 7.1)	
Moderate Hygiene	0.8 (0.2, 3.7)	
Good Hygiene	1 ^a	
No. Female Partners		.03
Less than 6	1 ^a	
Between 6 and 10	2.6 (0.6, 12.3)	
More than 10	3.8 (1.1, 12.6)	
Formal Education		.55
No Education	1.2 (0.1, 22.9)	
Primary Level	0.5 (0.1, 7.8)	
Secondary Level	0.7 (0.1, 18.1)	
Tertiary Level	1 ^a	
Familial Income		.86
<1 Minimal Wages	0.5 (0.1, 2.3)	
1–2 Minimal Wages	0.1 (0, 0.8)	
>2 Minimal Wages	1 ^a	

^aReference category; CI: confidence interval.