Carcinoma of the penis: a presentation of ten cases

Arroyo Carlos,1 Hernandez-Molina Jonathan,1 Soto-Vega Elena2

ABSTRACT

Objective: To report ten cases of carcinoma of the penis and evaluate their management at a university hospital.

Methods: A descriptive, retrospective study of patients that presented with penile cancer within the last five years at the Hospital Universitario de Puebla is presented. Only cases with histopathological diagnosis and complete case record were included.

Results: Ten patients with penile cancer with mean age of sixty-three years at time of diagnosis are presented. All were cases of epidermoid cancer. Disease was localized in the glans and prepuce in eight patients, in the base of the penis in one patient, and in the body of the penis in one patient. The most frequent presentation was a bleeding ulcer in seven patients and a verrucous lesion in three patients. Clinical stage was T1N0M0 in five patients, T2N0M0 in two patients, and advanced stage in three patients. Seven patients were managed with partial penectomy (three with inguinal lymphadenectomy), two with radical penectomy, and one with radiochemotherapy. Follow-up varied from two to fifty-three months with one death at six months from disease progression, one death at three months from sepsis, and one death at three years from lymph node metastasis. The remaining patients have had no evidence of tumor disease.

Conclusions: The present study results confirm the fact that early stage disease with adequate surgical treatment has good prognosis, concurring with similar encouraging results in the literature.

Keywords: Carcinoma of the penis, human papillomavirus, penectomy, Mexico.

RESUMEN

Objetivo: Presentar 10 casos de cáncer de pene y evaluar su manejo en un hospital de segundo nivel.

Métodos: Estudio retrospectivo y descriptivo de casos de cáncer de pene (CaP) en los últimos cinco años en el Hospital Universitario de Puebla, se incluyó solo casos con diagnóstico histopatológico y expediente completo.

Resultados: Se presentan 10 pacientes con CaP con edad promedio de 63 años, epidermoide en todos los casos. Su localización fue de ocho en glan- de y prepuce, uno en base y uno en cuerpo del pene. La presentación más frecuente fue una úlcera sangrante en siete y como lesión verrugosa en tres. El estadio clínico fue T1N0M0 en cinco, T2N0M0 en dos y tres avanzados. Manejados con falectomía parcial en siete (tres con linfadenectomía inguinal), dos con falectomía radical y uno con radioquimioterapia. Su seguimiento varió de dos a 53 meses con un finado a los seis meses por progresión, y otro a los tres meses por sepsis; uno con metástasis ganglionares falleció tres años después y el resto sin evidencia de enfermedad tumoral.

Conclusiones: Se confirma que los estadios tempranos con manejo quirúrgico adecuado tienen buen pronóstico, que reflejan resultados alentadores similares a la literatura.

Palabras clave: Cáncer de pene, virus de papiloma humano, falectomía, México.
INTRODUCTION

Carcinoma of the penis presents in individuals between fifty and seventy years of age, representing only 2-5% of urogenital tumors in men. However, its incidence is variable in certain countries on the American continents such as Puerto Rico and Brazil where incidence of neoplasias in men has been reported to reach 10%.1

Penile cancer has been associated with risk factors such as smoking, phimosis, deficient hygiene with accumulation of smegma, and chronic irritation. Some years ago it was suggested that neonatal circumcision had a protective effect against penile cancer. However, it has not been shown to be of real benefit. In the current literature, having multiple sexual partners has been accepted as a more important predisposing factor due to its association with sexually transmitted diseases, especially human papillomavirus (HPV). There are studies that show that a high percentage of penile cancer cases are associated with HPV infection, specifically serotypes 16 and 18 in 80% of primary tumors and 50% of lymph nodes.2,3 However, this is incongruent if the fact is taken into consideration that the frequency of this cancer is much lower when compared with the incidence of cervical cancer which is also associated with HPV infection and also the fact that there is elevated HPV infection incidence in asymptomatic men. The most common histological strain in penile cancer is epidermoid carcinoma and represents 95% of cases. The remaining 5% correspond to papillary carcinoma.

Ninety-six percent of epidermoid penile cancer are epithelial tumors and the remaining 4% are basocellular tumors, melanoma, Kaposi sarcoma (pathology with increased incidence due to its association with Acquired Immunodeficiency Syndrome [AIDS]), and in tumors that are secondary to leukemia or lymphoma, as well as anecdotal reports of metastasis originating in the kidney and prostate.4,5

Diagnosis: Penile cancer presents as a small visible verrucous or ulcerous lesion at the level of the glans or prepuce that at times is bleeding and frequently is associated with bacterial infection, producing a fetid odor with purulent secretion. Generally it is painless and many patients do not initially seek medical attention due to a lack of education as well as to cultural taboos. Early disease progression as well as superinfection result in frequent unilateral or bilateral inguinal adenopathy that can produce large fixed ulcerated suppurative masses that are adhered to deep planes. They can be accompanied with lymphedema of the pelvic and genital members. Symptoms associated with distant metastasis usually are present with advanced stage penile cancer.6,7

Initial dissemination route is through the superficial and deep preputial lymphatic vessels due to the fact that the glans and urethra drain the deep external inguinal lymph nodes. Hematogenous metastasis to solid organs presents in fewer than 10% of cases and the most frequent metastatic sites are the lung, liver, and bones. There are various clinical staging classifications and the TNM system is the most common in the literature (Table 1).

Diagnostic suspicion is clinical and due to appearance and the above-mentioned factors. Diagnosis is established at the moment of radical or partial penectomy, depending on clinical stage.

Given that there is no consensus in relation to systematically carrying out lymphadenectomy in penile cancer patients due to elevated morbidity (cutaneous necrosis, lymphatic fistula, and lymphedema) that the procedure entails, an attempt has been made to improve staging methods through the search for the sentinel lymph node in which the highest risk lymph node is determined as the first relay in identifying metastatic tumor cells through the use of lymphoscintigraphy or with coloring stains.8,9

Sentinel lymph node localization with nuclear medicine is carried out by means of intradermal injection around the tumor or in the skin of the distal axis of the penis with radioactive technetium sulfur colloid radioisotope. Four hours later the sentinel lymph node is looked for by means of scintigraphy during the surgical procedure. As an alternative, intradermal injections with methylene blue dye can be used. This has enabled modified partial lymphadenectomy to be carried out with the benefit of adequate staging without the adverse affects associated with extended radical lymphadenectomy.10

Treatment: Initial treatment is complete primary tumor resection by means of penectomy, attempting total tumor extirpation and microscopically verifying negative resection margins. Wide spectrum antibiotic administration for 4-6 weeks is recommended prior to lymphadenectomy or sentinel lymph node resection for the purpose of resolving the regional infectious component and thus possibly limiting complications inherent in lymphadenectomy.

The European Association of Urology (EAU) proposes that therapeutic success is related to primary tumor treatment by means of partial or radical penectomy together with unilateral or bilateral radical lymphadenectomy according to lymph node clinical staging (Table 2).11,12 Modifications that have been reported in the literature for carrying out partial lymphadenectomy attempt to reduce morbidity associated with dissection extension and skin devascularization that provoke cutaneous necrosis, infection, lymphedema, and deformity (30-50%).13,14

Mohs surgery is another surgical technique that enables dissection of cutaneous tumors in layers
If partial penectomy is chosen, it is recommended to carry out histological study by intraoperative freezing of surgical margins so that negative margin is assured with lymphadenectomy with no metastasis. 17

Systemic treatments in advanced stages are based on chemotherapy cycles of cisplatin with or without methotrexate resulting in a response rate of 68.5%. Modest results have also been achieved with the addition of 5-fluorouracile, bleomycin or methotrexate, with partial or complete remission results in up to 32% of cases. 18

According to the EAU, external radiotherapy and brachitherapy are indicated in very select penile cancer cases and they have achieved a complete response rate of 56% and 70%, respectively. However local failure rates are 40% and 16% with the option of rescue surgical resection that can restore local disease control. The most frequent complications associated with radiotherapy are meatal or urethral stenosis and telangiectasia formation. Prophylactic radiotherapy after complete antibiotic regimen is suggested in some centers for treating lymph nodes that are suggestive of neoplastic infiltration. However, this is not recommended in the case of clinically negative lymph nodes because it fails to prevent the development of posterior lymph node metastases and is associated with a high complication rate as well as a more difficult follow-up secondary to local fibrotic changes. 19

In regard to primary lesion, local disease recurrence rate with partial or total penectomy is between 0% and 7%. With conservative treatments such as radiotherapy and chemotherapy this increases to 50%. 20 Follow-up should be carried out every 4 months during the first two years, then every 6 months the third year, and then annually the fourth and fifth year. Recommended studies include detailed local and regional lymph node
physical examination together with abdominal and pelvic computed tomography and chest radiograph that are complementary studies for identifying pelvic or distant metastasis lymph nodes, particularly in tumors that are N2 or higher.

The majority of lymphatic recurrence is observed during the first two years and therefore strict surveillance is recommended in these cases since tumor growth is very fast and prognosis is related to size, number, and bilaterality of lymph nodes involved. Opportune follow-up is necessary for early diagnosis and treatment of metastases. Patients with local recurrence have a survival rate of approximately 7 years while disease progression to untreated lymph nodes is associated with poor survival rate that is generally less than 2 years.

A genetic factor has been sought that could explain the low incidence of penile cancer as well as its aggressive behavior in some cases. To date 62 microsatellital markers in six different chromosomes related to primary tumor appearance have been studied: 2q, 6p, 8q, 9p, 12q, and 17p13 as well as seven markers associated with lymph node metastasis: 3p, 6p, 6q, 8q, 9p, 11q, 12q, 17p, and 18q. In the future these could possibly establish prognosis parameters as well as certain genetic predisposition that would facilitate penile cancer diagnosis and probably its treatment. 21

## RESULTS

Mean age upon diagnosis was 63 years with a 38-81 year range. Among personal pathological past history were 4 patients with diabetes mellitus (DM), one with prostate cancer (CaP), and one with benign prostatic hyperplasia (BPH) managed with transurethral resection. In regard to histological diagnosis all patients presented with epidermoid penile cancer confirming that this histological strain is the most common. Histopathological pattern was well-differentiated in 50% of patients and moderately differentiated in the other 50%. Penile cancer was most frequently found in the glans and prepuce in 8 individuals, in the base of the penis in 1 case, and in the body of the penis in 1 case. It presented as a bleeding ulcer in 7 patients and as a verrucous lesion in 3 individuals. According to TNM classification 5 patients had stage T1N0M0 tumor, 2 patients had stage T2N0M0, 1 patient had stage T3N3Mx, and 1 patient had T4N2M0. One case was reported as stage T1NXMX upon not being able to determine the presence of distant metastasis to lymph nodes due to the fact that the patient was referred from another institution without adequate staging, in state of sepsis, with soft tissue infection, and with pneumonia that caused his death.

The treatment of choice in the majority of cases was partial penectomy in 7 patients (3 with inguinal lymphadenectomy). Two patients underwent radical penectomy with lymphadenectomy and 1 patient was managed with radiotherapy and chemotherapy with docetaxel polysorbate due to advanced stage T3N3. This patient died 6 months after diagnosis. Follow-up was limited due to the fact that the majority of patients did not go to out-patient consultation. Of the eight patients living, one presented with lymphatic fistula and lymphatic metastases that were managed with radiotherapy, controlling both pathologies, and
Table 3. Clinical characteristics of patients with penile cancer diagnosis.

<table>
<thead>
<tr>
<th>No. Px</th>
<th>Name</th>
<th>Age</th>
<th>Biopsy</th>
<th>TNM</th>
<th>Type of lesion</th>
<th>Past medical history pathologies</th>
<th>Treatment</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A.G.G.</td>
<td>38</td>
<td>moderately differentiated epidermoid Ca</td>
<td>T1,N0,M0</td>
<td>bleeding ulcer on glans</td>
<td>not stated</td>
<td>partial penectomy+ bilateral radical inguinal lymphadenectomy</td>
<td>NETA at 53 months</td>
</tr>
<tr>
<td>2</td>
<td>J.L.M.</td>
<td>51</td>
<td>well-differentiated epidermoid Ca infiltrated into prepuce</td>
<td>T1,N0,M0</td>
<td>ulcer on urethral meatus</td>
<td>perineum fracture 1998, circumcision</td>
<td>partial penectomy+ bilateral radical inguinal lymphadenectomy</td>
<td>NETA at 5 months</td>
</tr>
<tr>
<td>3</td>
<td>S.R.A.</td>
<td>56</td>
<td>well-differentiated epidermoid Ca</td>
<td>T1,N0,M0</td>
<td>wart in balanopreputial sulcus associated with vitiligo</td>
<td>not stated</td>
<td>partial penectomy+ bilateral radical inguinal lymphadenectomy</td>
<td>NETA at 10 months, left inguinal lymphatic fistula</td>
</tr>
<tr>
<td>4</td>
<td>F.C.F.</td>
<td>66</td>
<td>moderately differentiated epidermoid Ca</td>
<td>T1,N0,M0</td>
<td>wart on glans</td>
<td>DM</td>
<td>partial penectomy</td>
<td>NETA at 29 months</td>
</tr>
<tr>
<td>5</td>
<td>R.G.F.</td>
<td>62</td>
<td>well-differentiated epidermoid Ca</td>
<td>T2,N0,M0</td>
<td>ulcer on body of penis</td>
<td>proctitis, cystitis</td>
<td>partial penectomy+ radio-therapy</td>
<td>NETA at 8-month follow-up</td>
</tr>
<tr>
<td>6</td>
<td>V.R.J.</td>
<td>73</td>
<td>moderately differentiated invasive epidermoid Ca</td>
<td>T1,N0,M0</td>
<td>warts on prepuce and glans</td>
<td>DM</td>
<td>partial penectomy</td>
<td>NETA at 17 months</td>
</tr>
<tr>
<td>7</td>
<td>L.A.M.</td>
<td>75</td>
<td>moderately differentiated epidermoid Ca infiltrated into scrotum</td>
<td>T4,N2,M0</td>
<td>bleeding ulcer on prepuce and glans + inguinal adenopathy</td>
<td>recurrent penile Ca, fractures in extremities</td>
<td>radical penectomy+ radio-therapy+ left lymphadenectomy</td>
<td>NETA at 13 months</td>
</tr>
<tr>
<td>8</td>
<td>R.R.A.</td>
<td>81</td>
<td>well-differentiated epidermoid Ca</td>
<td>T2,N0,M0</td>
<td>ulcer on prepuce and glans infiltrating corpus cavernosum</td>
<td>DM, HTN, TURP</td>
<td>partial penectomy</td>
<td>NETA at 23 months</td>
</tr>
<tr>
<td>9</td>
<td>A.C.G.</td>
<td>56</td>
<td>well-differentiated epidermoid Ca</td>
<td>T1,Nx,Mx</td>
<td>ulcer on glans</td>
<td>DM</td>
<td>partial penectomy</td>
<td>deceased 3 months after diagnosis</td>
</tr>
<tr>
<td>10</td>
<td>A.M.T.</td>
<td>70</td>
<td>moderately differentiated epidermoid Ca</td>
<td>T3,N3,Mx</td>
<td>ulcer on glans</td>
<td>prostate cancer</td>
<td>radio-therapy + docetaxel chemo-therapy</td>
<td>deceased 6 months after diagnosis</td>
</tr>
</tbody>
</table>

NETA = No Evidence of Tumor Activity
patient died three years after initial management. Follow-up varied from 2–53 months with mean follow-up of 20 months. Table 3 shows the principal clinical characteristics of all patients.

### DISCUSSION

According to the results of the present study it was concluded that disease incidence in the city of Puebla is probably lower than that reported in the literature. Penile cancer tumor presentation in the present study was similar to that reported worldwide, having principally found early stage tumors in which T1, N0, M0 predominated. In relation to penile cancer treatment there is an important difference in techniques and methods utilized in developed countries. In Mexico the predominant tendency is toward radical procedures. Radical penectomy with lymphadenectomy is the most widely used due to lack of follow-up because patients do not go to control consultations. Sentinel lymph node localization by means of subdermal injection at lesion site with radioactive technetium is not often used due to its high cost.

The use of patent blue dye has not been widespread in the Mexican urological community due to skepticism in relation to definitive staging. Despite the justified usefulness of Mohs surgery in penile cancer treatment that enables healthy tissue preservation, it is not widely used in Mexico due to lack of infrastructure, surgical duration, and high cost of intraoperative histopathological studies.

Unlike developed countries where control follow-up is carried out as established in the literature, penile cancer patient follow-up is limited in Mexico due to the fact that patients abandon consultation, thus making it difficult to have adequate progression evaluation as well as to establish statistics on progression rate.

Further studies are needed in Mexico to be able to produce incidence statistics for this rare tumor and to be able to compare treatment regimens and patient progression in order to achieve a local consensus for the management of these patients.

### CONCLUSIONS

In Mexico penile cancer incidence appears to be lower than that reported in the international literature. However, there is no adequate case registration much less a national database to provide an accurate idea of this tumor incidence.

On the other hand, early diagnosis and radical treatment supported by the recommendations in the literature reduce morbidity and mortality in these cases. Regarding more conservative management based on the localization and biopsy of sentinel lymph node, it is a method not widely used in Mexico due to lack of diffusion and standardization, but its application could improve morbidity.

In Puebla more aggressive surgical treatments are carried out due to the fact that patients do not participate in out-patient control consultation, but disease-free survival rate appears to be very encouraging.

### BIBLIOGRAPHY