Neglected Carcinoma of Penis with Destruction of the Right Inferior Pubic Ramus Presenting As Right Hip Pain and Bleeding From Penis: Case Report and Review of the Literature Including Recommendations Of The Full Panel Of The International Consultation On Penile Cancer In November 2008

Corresponding Author:
Mr. Anthony K Venyo,
Urologist, Urology Department. North Manchester General Hospital, M8 5RB - United Kingdom

Submitting Author:
Mr. Anthony Kodzo - Grey Venyo,
Urologist, Urology Department. North Manchester General Hospital - United Kingdom

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Author(s): Venyo A K, Bakir E , Baiden-amissah K

Abstract

**Background:** Penile carcinoma is rarely found in developed countries in view of this a number of patients are unaware that their painless penile lumps could be malignant and delay in reporting their lesions may lead to progression of their tumours.

**Aims:** To report a neglected case of penile carcinoma which was reported after 2 years when complications had set in.

To review: the literature on carcinoma of penis; and the recommendations of the full panel of the international consultation on penile cancer in November 2008.

**Case Report:** A 72-years-old man was seen as an emergency due to severe bleeding from his penis. He had noticed a lump on his penis for two years but did not report it to any one because it was painless. For about ten days prior to his presentation he had been feeling unwell with loss of appetite; he also had right hip pain. On examination he was clinically found to be bleeding from an extensive penile carcinoma but there was no palpable inguinal lymph node. X-ray of pelvis and CT-scan of abdomen and pelvis confirmed the involvement as well as destruction of the right pubic ramus and part of the ischium by the penile tumour. Biopsy of the penile lesion confirmed a moderately differentiated squamous cell carcinoma of penis with no evidence of lymphatic or vascular invasion by the tumour. He had hypercalcaemia and was rehydrated as well as given Pamidronate to help lower the serum calcium level. He was transferred to the Regional Oncology Centre where he underwent toilet-partial penectomy and perineal urethrostomy. He was unfit to undergo chemotherapy, but borderline fit to undergo radiotherapy. His wound has healed and he has been listed for radiotherapy.

Literature review suggests that a high number of patients in this modern era are still reluctant to report their penile cancers for various reasons. The full panel of the International Consensus on Penile Cancer in November 2008 recommended that CT scan and MRI scan should not be done if the inguinal lymph nodes are not palpable. The patient did not have a palpable inguinal lymph node and there was no evidence of lymphatic or vascular invasion by the tumour. However, CT scan and plain X-ray showed involvement of the pubic ramus and ischium by the tumour.

**Conclusions:** In this modern era patients are still reluctant to report their penile lesions / penile cancers to their medical practitioners. This delay in reporting penile cancers early to medical practitioners is responsible for the progression of the penile cancers to advanced tumours that are not amenable to curative treatment. There is the need to educate all men to report any new and unusual penile lesions or lumps they have noticed early to their medical practitioners to allow for early diagnosis and provision of curative treatment. Even though the full panel of the International Consensus on penile Cancer suggested that there is no need for a CT-scan or MRI scan if there is no evidence of palpable inguinal lymph nodes, the fact that our patient did not have a palpable lymph node but had bony metastasis means that there should be another guideline which should read "in the absence of a palpable inguinal lymph node CT scan or MRI scan should be considered if the patient has bone / hip pain or if there is hypercalcaemia (GR C)".

Introduction

Carcinoma of the penis is rare in developed countries. The rarity of this condition, its variable clinical appearance, men's frequent hesitation to seek
treatment and inconsistency to follow-up often lead to long delay in its diagnosis and treatment. In addition, data on outcome of treatment have usually been derived primarily from retrospective studies; the number of patients in the retrospective studies, have been small and there are no randomized trials to define the optimal treatment.

Key areas of controversy that have existed in the management of carcinoma of penis include:

- The role of penile-sparing treatment versus more aggressive surgery (partial or total penile amputation)
- The need for prophylactic inguinal lymphadenectomy in men without palpable inguinal nodes
- Optimal management of men with locally advanced or metastatic disease. This manuscript reports a neglected case of carcinoma of penis with a review of the literature including recommendations of the full panel of the international consultation on Penile Cancer in November 2008.

**Case Report**

A 72-years-old man was seen in the surgical triage unit with a history of acute bleeding from his penis. He had been feeling unwell for about 10 days prior to his presentation in the hospital. He had also complained of right sided hip pain and loss of appetite to his General Practitioner who requested a plain X-ray of his pelvis. He had noticed a penile lump 2 years prior to his presentation but he did not tell anyone about it. He only previously rarely saw his General Practitioner because he did not have any serious ailments.

On examination he was noted to be pale and dehydrated otherwise his general examination was unremarkable. Examination of his respiratory and cardiovascular systems was normal. His abdominal examination was also normal and it was also noted that there was no evidence of any groin or femoral triangle lymph adenopathy. There was a bandage wrapped around his penis part of which was soaked with blood. On removing the dressing around the penis, the penis was noted to be very swollen all over especially on the dorsal two thirds of the whole length of the penis. There was acute bleeding from the ventral aspect of the penis near the corona with blood exuding out of a raw area where there has been loss of skin. On palpation the entire penis was noted to be indurated, oedematous with palpable irregular subcutaneous soft tissue mass without breach of the penile skin on the dorsal aspect of the penis extending towards the pubic area. There was foul smelling discharge around the raw area in the ventral aspect of the penis near the bleeding point. Pressure dressing was applied using fresh sterile bandage which stopped the bleeding. The size of the penile swelling was such that the external urethral opening was not easy to find.

A provisional diagnosis of extensive penile carcinoma with bleeding and penile infection as well as dehydration was made. He had the following initial investigations with the corresponding results:

- Full blood count – Haemoglobin 7.5 g/dL [normal range (13 – 18.0 g/dL)]; White Blood Cell Count - 20.2 x 10^9/L [normal range (4 – 11 x 10^9/L)]; platelets – 623 x 10^9/L [normal range (150 – 450 x 10^9/L)].
- Serum urea and Electrolytes- Sodium 135 m-mol/L [normal range (136-145 m-mol/L)]; Potassium 4.1 m-mol/L [ normal range (3.5-5.4 m-mol/L)]; Creatinine 122 u/mol/L [normal range (62 – 115 umol/L)]; Urea 7.6 m-mol/L [normal range (2.5 – 6.7 m-mol/L)]; eGFR (estimated glomerular filtration rate) 49 mL/minute [normal range (> 60 mL / minute)].
- Liver function test – Alkaline Phosphatase 140 u/L [normal range (30 – 150 u/L)]; ALT 22 u/L [normal range (10 – 35 u/L); Bilirubin 6 u-mol/L [normal range (3 – 21 u-mol/ L)]
- Coagulation screen – Normal
- Urine flow cytometry test: – white blood cell count 134 / uL [normal range (0 – 40 / uL)]; Red Blood Cell Count - 3695 / uL [normal range (0 – 35 / u/L)]; Epithelial cells – normal.
- Urine culture: < 10^4 mixed organisms / ml.
- MRSA screen - No Methicillin Resistant Staphilococcus Aureus grown

A plain X-ray of pelvis which he had taken at the request of his General Practitioner was reviewed and this revealed complete disruption or absence of the inferior right pubic ramus (as shown in illustration 1). He was rehydrated with Normal saline and was also given Intravenous Co-Amoxiclav 1.2 grams eight hourly which resulted in improvement of his renal function on subsequent renal function tests; the to the Regional oncology centre were: Sodium 137 m-mol/L; Potassium 3.7 m-mol/L; Creatinine 92 umol/L; Urea 5.2 m-mol/L; eGFR 68 mLs/min.

He underwent incisional biopsy of the penile lump in which multiple biopsies were taken (see illustrations 2, 3, and 4 for appearance of penis prior to biopsy). At the same a supra-pubic catheter was inserted into his urinary bladder to divert urine from his penis and to avoid urine soaking the penile dressing. Histological examination of the biopsy specimens was consistent.
with moderately differentiated squamous cell carcinoma of penis with no evidence of lymphatic or vascular involvement (see illustrations 5, 6, and 7).

He had CT scan of chest, abdomen and pelvis which revealed an extensive penile tumour which had extended proximally to into the right inferior pubic ramus which complete destruction of the bone; however, the left inferior pubic ramus was intact (see illustrations 8, 9 and 10). There was no evidence of lymph node involvement or any intra-abdominal or intra-thoracic involvement.

He had other investigations including: serum magnesium which was normal at 0.71 m-mol/L and 0.73 m-mol/L (normal range 0.7 – 1.0 m-mol/L; serum calcium which was recorded as 2.31 m-mol/L, 2.43 m-mol/L, 2.26 m-mol/ L (normal range 2.10 – 2.60 m-mol/L) with their corresponding corrected serum calcium at 2.65 m-mol/L, 2.81 m-mol/L and 2.62 m-mol/ L (normal range 2.10-2.60 m-mol/L) as well as corresponding serum albumin levels at 23 g/L, 21 g/L and 22 g/L (normal range 35-54 g/L). His serum calcium was noted therefore to be raised and he was treated with Pamidronate before he was referred and transferred to the Regional Oncology centre for treatment. A penile swab was taken for culture and this revealed a scanty growth of mixed skin organisms.

He underwent toilet-subtotal penectomy and urethral urethroplasty in the Regional Oncology centre. It was felt that he should receive a combination of chemotherapy and radiotherapy but after assessment he was found to be unfit to undergo chemotherapy and was borderline fit to undergo radiotherapy. After discussions with the patient he elected to receive palliative radiotherapy.

Discussion

Carcinoma of the penis is a malignant growth which is found on the skin or in the tissues of the penis. A squamous cell carcinoma usually originating in the foreskin or glans penis is by far the most common type and this occurs in 9 out of 10 cases [1]. Primary epithelial squamous cell carcinoma (SCC) has been reported by Burgers and associates [2] to account for 95% of penile malignancies. Other histologic types (e.g., soft tissue sarcomas, urethral tumours, lymphomas, basal cell carcinomas, metastases) are extremely rare [2, 3, 4, 5].

Penile cancer is rare in industrialized countries. For example the incidence of penile cancer in the United States of America was 0.58 per 100, 000 between 1993 and 2002, based upon data from the Surveillance, Epidemiology and End Results (SEER) database [6].

In contrast, penile carcinoma is reportedly a far more serious health problem in less developed areas of the world including some parts of Africa, Asia, and South America. In those areas, it has been reported that carcinoma of the penis can account for 10 to 20 percent of all malignancies in men [7, 8, 9, 10].

Penile carcinoma can be caused by phimosis and poor hygiene [11]. Circumcisions of newborns (e.g. Jews) results in almost 100% protection, and with adolescent circumcision [7, 8, 9, 10].

The development of penile carcinoma has long been associated with poor hygiene and exposure to irritants, carcinogens, or possible viral pathogens. In particular, the organism Mycobacterium smegmatis has been shown to convert sterols present in smegma to substances that have been shown to be carcinogenic in mice. In addition, infection with HPV-16 or HPV-18 has been associated with up to 60 percent of penile and cervical carcinomas, suggestive of a venereal basis for both malignancies. Penile and urethral condyloma, has been identified in up to 55% of sexual partners of women with cervical carcinoma. On the other hand, sexual partners of men with penile carcinoma have a three-fold higher incidence of cervical carcinoma. Malignant transformation of HPV-infected cells is thought to result from the inactivation of tumour suppressor gene proteins (p53 and Rb) by viral gene products E6 and E7 [12].

The usual presenting symptoms of carcinoma of penis include: redness, irritation, a sore on the penis or a lump on the penis [13]. Men with the aforementioned symptoms have been advised to consult a doctor [13]. Lesions of the penis that could be cancerous can be divided into the following groups:

1. Precancerous Dermatologic lesions
2. Carcinoma in situ (Bowen Disease, Erythroplasia of Queyrat)
3. Invasive Carcinoma of the penis.

Carcinoma of penis can be staged using the Jackson’s staging or the TNM staging method. The Jackson’s staging is system is summarized as follows:

Stage I – Cancer has only affected the glans penis and / or foreskin.
Stage II – Cancer has spread to the shaft of the penis.
Stage III – Mobile (operable), inguinal lymph nodes.
Stage IV – Fixed (inoperable), inguinal lymph nodes, and / or distant metastasis.
Recurrence – Cancer that has returned after treatment.

The TNM classification of carcinoma of penis (“T” refers to the primary tumour; “N” refers to the lymph node; “M” refers to all other distant metastases is summarized as follows:

The primary penile tumour stages
• Tx - Primary tumour not assessed
• To - No evidence of primary tumour
• Ta – Non-invasive verrucous carcinoma
• Tis – Carcinoma in situ
• T1 - Tumour invades subepithelial connective tissue
• T2 – Tumour invades corpus spongiosum or cavernosum
• T3 – Tumour invades urethra or prostate
• T4 – Tumour invades other adjacent structures.

Secondary node involvement of penile cancer is staged as follows:
• Nx - Lymph node status unknown
• N0 - No lymph node metastases
• N1 - Metastasis in single superficial inguinal lymph node
• N2 - Metastases in multiple or bilateral superficial inguinal lymph nodes
• N3 - Metastases in any lymph nodes

(13% of all patients have involved inguinal lymph nodes at the time of presentation [can be found at www.ewingurologyclinic.co.uk])

Distant metastases from penile carcinoma are staged as:
• Mx – Metastatic status unknown
• Mo – No distant metastases
• M1 Distant metastases

2.5% of all patients have distant metastases at the time of presentation. 8% were un-staged can be found at www.ewingurologyclinic.co.uk

An alternative American Joint Committee on Cancer (AJCC) staging of penile cancer is also in use even though the TNM classification is becoming more popular. The AJCC staging of penile cancer is outlined below:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>TNM equivalent</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Non-invasive verrucous</td>
<td>Any T N3 M0</td>
</tr>
<tr>
<td>Ta</td>
<td>No Mo Carcinoma in situ</td>
<td>Any T any N M1</td>
</tr>
<tr>
<td>Tis</td>
<td>Tumour invades sub-epithelial tissue</td>
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<tr>
<td>T1</td>
<td>Tumour invades corpus spongiosum or cavernosum</td>
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<tr>
<td>T1</td>
<td>N1 Mo</td>
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<tr>
<td>T2</td>
<td>No Mo</td>
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<tr>
<td>T2</td>
<td>N1 Mo</td>
<td></td>
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<tr>
<td>3</td>
<td>Tumour invades urethra or prostate</td>
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<tr>
<td>T1</td>
<td>N2 Mo</td>
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<td>T2</td>
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<td>T3</td>
<td>N2 Mo</td>
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</tr>
<tr>
<td>4</td>
<td>Tumour invades other adjacent structures</td>
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<tr>
<td>T4</td>
<td>any N Mo</td>
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Dilner and associates [14] reviewed the epidemiology of invasive cancer of the penis based on scientific publications identified by a Medline search from 1966 to 2000 for keywords penis/penile, cancer/carcinoma and risk as well as the cited references in the identified papers. Strong risk factors (OR >10) identified by case-control studies included phimosis, chronic inflammatory conditions such as balanopostitis and lichen sclerosus et atrophicus and treatment with psoralen and ultraviolet A photochemotherapy (PUVA). A consistent association was found between penile cancer and smoking that was dose-dependent and not explained by investigated confounding factors such as sexual history. Sexual history and self-reported history of condyloma were associated with 3-5-fold increased penile cancer risk. Cervical cancer in the wife was not consistently associated with carcinoma of penis in the husband. Circumcision was associated with penile cancer risk in a 3-fold decreased risk, albeit 20% of penile cancer patients had been circumcised neonatally. In a large number of case series, human papilloma virus (HPV) DNA was identified in penile neoplastic tissue. In penile intraepithelial neoplasia, between 70 and 100% of lesions were HPV DNA positive, on the other hand penile cancer was positive in 40-50% of cases. One prospective study and few serological case-control studies also identified an association between HPV type 16 and penile cancer risk. An association between penile cancer risk and HPV prevalence in the population was also suggested by ecological studies. Dilner and associates [14] concluded that the evidence on risk factors for penile cancer suggests that preventive measures that could be considered include prevention of phimosis, treatment of chronic inflammatory conditions, limiting PUVA treatment, smoking cessation and prophylactic prevention of HPV infection.

Penile carcinoma is mainly a localised disease (39%) with carcinoma-in-situ making up 37% and regional disease 13%. Distant metastasis from haematogenous spread is rare (2.3%) and the mean life span of those with distant metastasis is 7.4 months [15].

A number of cases of penile carcinoma associated with metastases have been reported including: kidney, adrenal gland, retroperitoneal lymph nodes, lung, brain, dorsal spine, meninges, and the orbit [16, 17, 18, 19]. The aim of this case report and the lengthy review is to highlight a number of important features of the natural history and patient management in penile cancer. Firstly, even in this modern age a number of
patients are unwilling to consult physicians early about their penile cancer. The reason behind this may lie in the fact that the diagnosis of penile cancer could be devastating to a man and his spouse as well as the fear of cancer is heightened by the prospect of penile amputation [20].

Soria and associates [21], have found, in a large series of penile cancer patients, a long delay before the diagnosis with 13.7% of patients having symptoms which lasted more than a year prior to the initiation of definitive therapy.

Such a delay stems from ignorance, fear, embarrassment, neglect and guilt, which can be ameliorated somewhat by educating the public about personal hygiene, including the early treatment of phymosis, and about how to recognize early signs of penile cancer [21, 22].

In our case, the patient noticed his penile lump 2 years earlier at a stage when the lesion was amenable to treatment by either local excision or at worst partial penectomy. The patient has a close relative who is a health-care worker but still the patient did not mention the lesion to this relative because there was no pain associated with the lesion. The patient ignored the lesion for two years until he developed metastatic disease as well a complication of bleeding. This patient noticed his lump at a stage where he could have had curative treatment but waited for two years and presented at a stage where he could not have curative treatment and his prognosis is poor. This case confirms that despite the fact that we are in a modern internet era with televisions all over the world there is a great need and demand for improvement in health education in order to encourage patients to report early all unusual lumps to their medical practitioners whether the lumps are or not associated with pain.

With regard to treatment of primary penile lesions, all penile lesions present which have been present for more than 3 weeks should undergo biopsy with deep margin to ensure proper staging [12]. Simple circumcision may be enough to treat lesions confined to the prepuce. Patients with superficial tumours (stages Tis and T1) can be managed with penile-salvage techniques using Mohs microresection, laser photocoagulation (CO2 or Nd-YAG), or radiation (external- beam, or, brachytherapy) with approximately recurrence rates of 6%, 25%, and 21% respectively [12]. Large stage T1 tumours and T2 lesions of the glans or penile shaft should be treated by partial penile amputation; ensuring a 2-cm tissue margin proximal to the tumour, in view of the fact that local wedge resection has a 50 percent recurrence rate versus 0% to 8% with partial penectomy. In the case of bulky T3 and T4 tumours or if the location of the tumour is such that amputation would leave a penile stump inadequate for voiding or sexual activity, a total penectomy with perineal urethrostomy is preferred [12].

Inguinal node metastasis is regarded as a more important prognostic factor than tumour grade. Even though 55% of patients present with palpable inguinal lymph nodes, half of these are tumour free on histological examination [12]. In view of this it has been said that all patients with inguinal adenopathy should be treated with 6 weeks of oral antibiotics after undergoing penectomy to segregate those patients with true metastases [12]. A quarter of patients with without palpable adenopathy will have nodes containing metastases. Patients with palpable inguinal with lymph adenopathy despite oral antibiotic therapy should undergo superficial and deep ipsilateral ilioinguinal lymphadenectomy [12]. In the case when lymph nodes are positive on one side the contralateral nodes are involved in 50% of cases, and iliac nodes involved in a third of cases. In view of this it has been recommended that these patients should also undergo a contralateral superficial inguinal lymphadenectomy [12]. Additionally, many experts would argue for the performance of an ipsilateral pelvic lymph node dissection. The timing of surgery (simultaneous versus asynchronous) remains controversial. Though approximately 20% of patients with non palpable inguinal lymph node harbour microscopic metastasis, considerable controversy exists in relation to the performance of a prophylactic inguinal lymphadenectomy due to its significant morbidity. However, recent reports indicate that survival is significantly improved in patients who undergo a prophylactic (5- year survival, 88%) versus delayed (5- year survival 38%) inguinal lymphadenectomy. Even though no strict criteria have been established, indications for prophylactic superficial inguinal lymphadenectomy inpatients with a normal inguinal physical examination include invasive T1-T3 lesions or high tumour grade [12].

The margin of dissection of the inguinal lymphadenectomy, include the inguinal ligament, adductor longus, Sartorius, and the base of the femoral triangle [12]. The fascia lata separates the superficial from the deep inguinal lymph node compartment. The development of modified dissection involving limited surgical margins and the preservation of the saphenous vein may incur less morbidity. The Sartorius muscle can be detached from the anterior superior iliac spine and repositioned or more medially to protect the femoral vessels. Alternatively, a Gracilis or rectus muscle flap can be used to fill large defects.
after resecting large masses, thus preventing vessel erosion and skin necrosis. The presence of pelvic node disease portends a very poor prognosis [12].

Tan and associates [23] retrospectively analyzed the clinical data of 58 cases of pathologically confirmed penile squamous cell carcinoma. They reported that based upon the Jackson Staging, 25 of the 58 cases fell into stage I, 18 Stage II, 11 Stage III, and 3 Stage IV. Fifty three of the patients were treated by surgery of who 43 underwent limited resection of the tumour or partial amputation of the penis, and the other 10 underwent total penis amputation plus perineal urethroscopy and clearance of lymphoglandulae iliacae and inguinal lymph nodes, with the lymphoglandulae iliacae positive in 1 case and the inguinal lymph nodes positive in all. Thirty – seven cases received neoadjuvant hormonal therapy (thermotherapy plus chemotherapy) and combined postoperative chemotherapy, 12 postoperative chemotherapy only, and 4 merely surgery. Five of the total number underwent chemotherapy and/or radiotherapy without surgery. The 2-5 years follow-up of 48 patients found recurrence in 4 cases of partial penis amputation within 2 years, 4 deaths within 2 years, 7 deaths from 2 to 5 years. The 2- and 5-year survival rates were 91.7% and 77.1% respectively. Ten of the cases were lost to follow-up. They concluded that surgery + neoadjuvant hormone therapy + postoperative chemotherapy is an effective method for treating penile squamous cell carcinoma of penis, but whether it can reduce the recurrence of penile squamous cell carcinoma and improve the survival of the patients remains to be further studied.

Zheng and co-workers [24] conducted a retrospective review of 46 patients who were treated for penile cancer between January 1996 and January 2005; Forty-four patients had squamous cell carcinoma; one had Paget disease, and one had verrucous carcinoma. They reported that thirty nine patients had Paget disease, and one had verrucous carcinoma. They used a monoclonal mouse antibody directed against CD34 antigen. Only 61 (30 with and 31 without metastasis) patients had good staining properties and were included. After immunostaining, the entire tumour section was scanned microscopically at low power (x40) to identify hot spots within the tumour and at its periphery. Individual tumour microvessels were then counted under high power (x200) to obtain a vessel count in a defined area, and the mean of the 3 highest microvessel counts was taken as the microvessel density (MVD). Microvessel counting was performed using a computer-aided image analysis system. The nodal status was based on histologic examination or an uneventful follow-up ≥ 2 years. They reported that the 5-year overall survival (OAS) was 75.3% and 78.1% at 2 and 5 years after PTE. Al-Najar and associates [26] examined the potential effect of tumour-induced angiogenesis in squamous cell carcinoma of the penis as a possible prognostic factor. Immunohistochemistry was performed to detect microvessels in tumour samples of 64 patients with squamous cell carcinoma of the penis. They used a monoclonal mouse antibody directed against CD34 antigen. Only 61 (30 with and 31 without metastasis) patients had good staining properties and were included. After immunostaining, the entire tumour section was scanned microscopically at low power (x40) to identify hot spots within the tumour and at its periphery. Individual tumour microvessels were then counted under high power (x200) to obtain a vessel count in a defined area, and the mean of the 3 highest microvessel counts was taken as the microvessel density (MVD). Microvessel counting was performed using a computer-aided image analysis system. The nodal status was based on histologic examination or an uneventful follow-up ≥ 2 years. They reported that the 5-year overall survival (OAS) was 75.3% and 78.1% at 2 and 5 years after PTE.
intratumoral MVD (log rank P = 0.99). The mean intratumoral MVD was 32.35 (3.16), 37.94 (3.35), and 62.66 (5.47) in T1, T2, and T3 respectively (ANOVA P = 0.0006), with increasing tendency. The mean peritumoral MVD was 55.91 (5.60), 56.8 (4.00), and 78.86 (8.71), respectively (P = 0.06). No correlation between MVD lymph node status and tumour grade was seen (P>0.05). They concluded that in their group of patients, a high peritumoral MVD was associated with a better 5-year OAS. However, for a reliable and reproducible assessment of tumour angiogenesis in penile squamous cell carcinoma, validation procedures and quality control protocols are mandatory.

Minardi and associates [27] investigated D2-40 immunohistochemical expression in tissue specimens from 39 patients with squamous cell carcinoma of the penis who underwent partial or total penectomy between 1987 and 2008. Patient age, tumour size, and grade, D2-40-positive lymphatic vessel density in intratumoral, peritumoral, and normal tissue; cell positivity for D2-40 in intratumoral and normal tissue; and D2-40 staining intensity and distribution were analyzed and correlated with disease specific survival. Analysis of D2-40-positive lymphatics disclosed that mean lymphatic vessel density was greater in peritumoral tissue than in intratumoral and normal tissue and lower in patients with lymph node metastasis than in those without lymph node metastasis. The receiver operating characteristic curve showed that an intratumoral lymphatic vessel density greater than 2.0 had 83.3% sensitivity and 78% specificity in predicting lymph node metastasis. Analysis of immunoreactivity showed cytoplasmic D2-40 positivity in intratumoral and normal tissue in 89.7% and 65.5% of patients respectively. A strong correlation emerged between grade of cell differentiation and D2-40 immunoreactivity in intratumoral tissue; in particular, 88.9% of tumours with weak podoplanin expression were G1, whereas, strong cellular immunoreactivity was detected in 83.3% of G3 patients (P = 0.03, chi-square test). A significant correlation was also noted between pattern of reactivity and tumour grade because the basal layer was positive in patients with undifferentiated tumours (100% of G3) and in 72.2% of G1 tumours (P = .021, chi-square test). They concluded that D2-40 seems to be a useful marker for the development of node metastasis in squamous cell carcinoma of the penis, although validation in a larger series is required to confirm its predictive value [27].

Metastatic penile cancer is moderately sensitive to chemotherapy. Partial responses are most common, occurring in approximately 64% of patients while complete responses occur in less than 15% of patients. Regimens that have been studied include methotrexate, bleomycin and cisplatin (MBP), vinblastine, bleomycin and methotrexate (VBM), and cisplatin with 5-fluorouracil [28]. Our patient did not have any palpable inguinal lymph nodes but he had metastatic disease in the form of involvement and destruction of the right inferior pubic ramus. Histological examination of the tumour revealed no evidence of lymphatic or vascular involvement by tumour. It would be said that the involvement of the inferior pubic ramus has been a result of direct invasion of the pubic ramus and part of the ischiium. The patient also had hypercalcaemia. Heyns and associates [29] reported on a comprehensive literature study which was conducted to evaluate the levels of evidence (LEs) in publications on the diagnosis and staging of penile cancer. Recommendations from the available evidence were formulated and discussed by the full panel of the International Consensus on Penile Cancer in November 2008. The final grades of recommendation (GRs) were assigned according to the LE of the relevant publications. The ensuing consensus recommendations were accepted:

- Fine needle aspiration cytology should be performed in all patients (with ultrasound guidance in those with non palpable inguinal nodes). If the findings are positive, therapeutic rather than diagnostic, inguinal lymph node dissection (ILND) can be performed (GRB).
- Antibiotic treatment for 3-6 weeks before (ILND) in patients with palpable inguinal nodes is not recommended (GRB).
- Abdominopelvic computed tomography (CT) and magnetic resonance imaging (MRI) are not useful in patients with nonpalpable inguinal nodes. However, they can be used in those with large, palpable inguinal nodes (GRB).
- The statistical probability of inguinal micrometastases can be estimated using risk group stratification or a risk calculation nomogram (GR B). Surveillance is recommended if the nomogram probability of positive nodes is • Surveillance is also recommended if the primary lesion is grade 1, pTis, pTa (verrucous carcinoma), or pT1, with no lymphovascular invasion and clinically nonpalpable inguinal nodes, but only provided the patient is willing to comply with regular follow-up (GR B).
- In the presence of factors that impede reliable surveillance (obesity, previous inguinal surgery, or radiotherapy) prophylactic ILND might be a preferable option (GR C).
- In the intermediate-risk group (nomogram probability
1-5 [10% - 50%] or primary tumour grade 1-2, T1-T2, cN0, or lymphovascular invasion), surveillance is acceptable, provided the patient is informed of the risks and is willing and able to comply. If not, sentinel node biopsy (SNB) or limited (modified) ILND should be performed (GR B).

- In the high-risk group (nomogram probability > 5 [50%] or primary tumour grade 2-3 or T2-T4 or cN1-N2, or with lymphovascular invasion), bilateral ILND should be performed (GR B). ILND can be performed at the same time as penectomy, instead of 2-6 weeks later (GR C).
- SNB based on the anatomic position can be performed provided the patient is willing to accept the potential false-negative rate of
- Limited ILND can be performed instead of complete ILND to reduce the complication rate, although the false-negative rate might be similar to that of anatomic SNB (GR C).
- Frozen section histologic examination can be used during SNB or limited ILND. If the results are positive, complete ILND should be performed ipsilaterally (GR B).

- In patients with histologically confirmed inguinal metastases involving >/=2 nodes on one side, contralateral limited ILND with frozen section analysis can be performed, with complete ILND if the frozen section analysis findings are positive (GR B).
- If clinically suspicious inguinal metastases develop during surveillance, complete ILND should be performed on that side only (GR B), and SNB or limited ILND with frozen section analysis on the contralateral side can be considered (GR C).
- Endoscopic ILND requires additional study to determine the complication and long-term survival rates (GR C).
- Pelvic lymph node dissection is recommended if >/= 2 proven inguinal metastases, grade 3 tumour in the lymph nodes, extranodal extension (ENE), or large (2-4 cm) inguinal nodes are present, or if the femoral (cloquet’s) node is involved (GR C).
- Performing ILND before pelvic lymph node dissection is preferable, because pelvic lymph node dissection can be avoided in patients with minimal inguinal metastases, thus avoiding the greater risk of chronic lymphedema (GR B).

- In patients with numerous or large inguinal metastases, CT or MRI should be performed. If grossly enlarged iliac nodes are present, neoadjuvant chemotherapy should be given and the response assessed before proceeding with pelvic lymph node dissection (GR C).
- Antibiotic treatment should be started before surgery to minimize the risk of wound infection (GR C).

- Perioperative low-dose heparin to prevent thromboembolic complications can be used, although it might increase lymph leakage (GR C).
- The skin incision for ILND should be parallel to the inguinal ligament, and sufficient subcutaneous tissue should be preserved to minimize the risk of flap necrosis (GR B).
- Sartorius muscle transposition to cover the femoral vessels can be used in radical INLD (GR C).
- Closed suction drainage can be used after ILND to prevent fluid accumulation and wound breakdown (GR B).
- Early mobilization after ILND is recommended, unless a myocutaneous flap has been used (GR B).
- Elastic stockings or sequential compression devices are advisable to minimize the risk of lymphedema and thromboembolism (GR C).
- Radiotherapy to the inguinal areas is not recommended in patients without cytologically or histologically proven metastases nor in those with micrometastases, but it can be considered for bulky metastases as neoadjuvant therapy to surgery (GR B).
- Adjuvant radiotherapy after complete ILND can be considered in patients with multiple or large inguinal metastases or ENE (GR C).
- Adjuvant chemotherapy after complete ILND can be used instead of radiotherapy in patients with >/= 2 inguinal metastases, large nodes, ENE, or pelvic metastases (GR C).
- Follow-up should be individualized according to the histopathologic features and the management chosen for the primary tumour and inguinal nodes (GR B).
- In patients with numerous or large inguinal metastases, CT or MRI should be performed. If grossly enlarged iliac nodes are present, neoadjuvant chemotherapy should be given and the response assessed before proceeding with pelvic lymph node dissection (GR C).
- Antibiotic treatment should be started before surgery to minimize the risk of wound infection (GR C).

Conclusions

In this modern era patients are still reluctant to report their penile lesions / penile cancers to their medical practitioners. This delay in reporting penile cancers...
early to medical practitioners is responsible for the progression of the penile cancers to advanced tumours that are not amenable to curative treatment. There is the need to educate all men to report any new and unusual penile lesions or lumps they have noticed early to their medical practitioners to allow for early diagnosis and provision of curative treatment. Even though the full panel of the International Consensus on penile Cancer suggested that there is no need for a CT-scan or MRI scan if there is no evidence of palpable inguinal lymph nodes, the fact that our patient did not have a palpable lymph node but had bony metastasis means that there should be another guideline which should read “in the absence of a palpable inguinal lymph node CT scan or MRI scan should be considered if the patient has bone / hip pain or if there is hypercalcaemia (GR C)”.

References

1. Cancer Research UK. Types of Penile Cancer2008 06 04b can be found at http://cancerhelp.org/type/penile-cancer/about/types-of-penis-cancer
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Illustrations

Illustration 1

Illustration 1: Plain X-ray of pelvis showing destruction of the right inferior pubic ramus due to tumour involvement infiltration; part of the ischium was also involved.

Illustration 2

Illustration 2: Showing penis just before biopsy of tumour was taken
Illustration 3

Illustration 4 showing another view of the penis before biopsy of penile tumour

Illustration 4

Illustration 4: Showing another view of the penis just before biopsy of the penile tumour
Illustration 5

Illustration 5 (X4) A section from the penile biopsy showing Squamous cell carcinoma in the dermis

Illustration 6

Illustration 6: (X20) Moderately differentiated squamous cell carcinoma of penis. Sheets of malignant squamous cells are infiltrating the dermis
Illustration 7

Illustration 7: (X40) Moderately differentiated squamous cell carcinoma of the penis. Mitotic figures are present in the infiltrating malignant cells

Illustration 8

Illustration 8: CT scan showing tumour in penis and tumour infiltrating and destroying the right inferior pubic ramus; left inferior pubic ramus is intact
Illustration 9

Illustration 9: Another view of the CT scan showing tumour in the penis and tumour infiltration and destruction of the right inferior pubic ramus

Illustration 10

Illustration 10: Another view of CT scan showing tumour in the penis with involvement and destruction of right inferior pubic ramus by tumour; ischium partly involved by tumour
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