

A review of penile metastasis

Luigi Mearini,¹ Renato Colella,² Alessandro Zucchi,¹ Elisabetta Nunzi,¹ Carlo Porrozzì,¹ Massimo Porena¹

¹*Urology Department;* ²*Pathological Anatomy and Histology Department, University of Perugia, Italy*

Abstract

Penile cancer as primary disease is relatively rare in developed countries. The penis is a rare site of metastases in spite of its rich vascularization. Approximately 500 cases have been reported in the literature; almost 70% of primary lesions are of pelvic origin (from genitourinary or recto-sigmoid primary tumors). We describe a case of penile metastasis from lung cancer. The rarity of the event prompted us to also explore related reviews and discuss the incidence, pathophysiology, diagnosis and therapy of penile secondary cancer.

Introduction

Penile cancer is a relatively rare disease in developed countries with an annual incidence of less than 1 case per 100,000 person-years in Western populations.^{1,2} It accounts for up to 10% of cancers in men in some parts of Asia, Africa and South America.

As primary disease, penile cancer typically occurs in later life, at a mean age of 68 years in the USA.³ Factors associated with increased risk of primary penile cancer include low socio-economic status, poor or lack of penile hygiene, phimosis and chronic penile inflammation,

cigarette smoking, human papillomavirus (HPV) infection and/or multiple sexual partners, and infection by acquired immune deficiency syndrome (AIDS). Each of the tissues in the penis contains several types of cells and different types of penile cancer can develop from each kind of cell.

However, considering the risk factors and causes, almost all penile primary cancers start in the skin cells of the penis. According to histology, squamous cell carcinomas are the most common type of penile cancer, accounting for 93% of all reported tumors. Typical squamous cell carcinoma accounts for 50-60% of penile cancer. Verrucous carcinoma is the most frequent subtype of squamous cell carcinoma, followed by condylomatous warty, papillary and basaloid carcinoma. Other epithelial cancers include basal cell and transitional cell carcinomas arising from the urethra. Rare histological types include adenocarcinoma, melanoma and Kaposi sarcoma.

Secondary penile cancer, as a consequence of metastatic disease, is an extremely rare event. This is in spite of the rich vascularization of the penis and the rich vascular communication between penis and the neighboring pelvic organs. Effectively, most cases of secondary penile malignancy have been found to originate from pelvic primary sites, usually associated with disseminated disease. Clinical manifestations of penile metastases vary widely and usually include penile nodules, malignant priapism and skin lesions. Secondary penile cancer is usually a deep disease which does not develop as a superficial skin lesion.

We present an interesting case of penile metastasis as first manifestation of a lung adenocarcinoma. We also review the literature on penile metastases, and discuss its incidence, pathophysiology, diagnosis, therapy and prognosis.

Case Report

A 62-year old man, an ex-heavy smoker, with diabetes and chronic heart ischemia, presented with a 4-month history of sharp, burning and refractory penile pain in both a flaccid state and erection, associated with hardening of the glans and penile tip and stranguria. Pain had heavily impacting on daily life and sleeping, and had been treated with anti-inflammatory drugs, analgesic and corticosteroid, none of which relieved the pain symptoms. On physical examination, the patient had a normal penile shaft and glans, with pain on palpation of a nodule involving glans, distal urethra and the distal tips of corpora cavernosa, causing distal urethral stricture. Penile ultrasound showed a hypoechoic area of 24×19 mm involving the glans and corpora cavernosa associated with peripheral hypervascularity. Magnetic resonance imaging (MRI) scan of the penis was performed. This showed a lesion bilaterally located in the distal corpus cavernosum, with an extension to distal corpus spongiosum. The lesion was characterized by low signal intensity on both T1 and T2 weighted images. After Gadolinium administration it showed prominent contrast enhancement; pelvic MRI was negative.

Given the urgency of the presentation and the presence of urethral

Correspondence: Luigi Mearini, Urology Department, University of Perugia, Sant'Andrea delle Fratte - 06100 Perugia, Italy.
Tel. +39.075.578.4252 - Fax: +39.075.578.4416. E-mail: luigi.mearini@tin.it

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stricture, after accurate informed consent the patient underwent penile exploration to obtain histopathological diagnosis and urethral clearing; a frozen section of surgical margin showed foci of adenocarcinoma in the corpus cavernosum (Figure 1).

The patient underwent partial amputation with penile resurfacing. Histologically, the nodule was composed of glandular structures lined by atypical cells (Figure 2A and B). Immune-histochemical investigation showed diffuse cellular positivity for cytokeratin 7 and TTF1 (Figure 2C and D) while cells were negative for cytokeratin 20, prostate specific antigen (PSA), PSAP and CDX2. These findings were consistent with the diagnosis of penile metastases of lung adenocarcinoma.

A chest X-ray showed a primary 7-cm right lobe tumor while a bone scan showed multiple metastases to the bones. The patient and his family were counseled extensively on the extent of the disease as well as the treatment options. He was then referred to the Oncology Department for further medical management (carboplatin 600 mg+pemetrexed 850 mg+dexamethasone 8 mg).

At 7-month follow up, despite optimal local control, the patient developed a superior vena cava syndrome and died of heart failure.

Review of the literature

Search strategy

A literature search was carried out using MEDLINE®/Cochrane libraries from 1940 to date using the following search items: *penis, penile metastasis, secondary malignancy, malignant priapism*. No language restrictions were imposed. When necessary, we contacted the authors to obtain any relevant information we found to be missing from published papers.

The search included original articles, review articles and editorials and these were reviewed in order to select relevant articles.

In March 2012, the search had produced 309 references of which 24 were reviews.

Discussion

Secondary malignancy of the penis as metastatic disease is a rare clinical entity, despite the rich vascularization of this organ even in flaccidity, with an increase in penile arterial blood flow to approximately 25 to 60 times that of the flaccid state during the rapid period of tumescence. Furthermore, at full rigidity, there is an entrapment of approximately 100 mL of blood which physiologically occurs four to five times per night, lasting 30-45 min. Therefore, there is a discrepancy between the relative blood supply and the rarity of the penis as site of secondary malignancy. According to the seed and soil hypothesis, and according to the fact that the site of metastasis is determined not only by the characteristics of the neoplastic cells but also by the microenvironment of the host tissue, the penis does not provide the perfect environment (soil) for neoplastic seeding. Furthermore, the rich communications between arterial inflow and venous outflow could explain the difficulty in cell seeding in normal conditions. However, when the outflow is impaired by venous or lymphatic occlusion, such as in the presence of tumor in the neighboring genito-urinary organs or in massive pelvic disease, the process of seeding could be facilitated.

Most metastatic lesions originate from the neighboring genito-urinary and pelvic organs, mainly bladder, prostate and rectum-sigmoid (28.6%, 27.9% and 12.2%, respectively). However, many primary sites have been described, including kidney, the hematologic system, lung, testis and other sites, totalling 504 reported cases to date (Table 1).

The earliest report of secondary penile malignancy was by Eberth in 1870. He reported a case of unusual metastasis from an adenocarcinoma of the rectum.⁴ In 1872, Roberts reported the first case of penile secondary malignancy as metastasis from a genitourinary tumor.⁵

The penis has a rich vascularization which increases during tumescence, and with respect to the arterial and venous systems it is an end organ. Despite this, the penis is a rare site of secondary malignancy. In 1956, Paquin hypothesized and described the possible mechanisms by which tumor cells spread to the penis.⁶ Generally speaking, we can only hypothesize the exact way in which they spread for each case and for each different primary tumor. In fact, penile secondary malignancy is usually associated with disseminated disease in which every metastatic mechanism could play a key role and each different primary tumor tends to metastasize according to different patterns. For example, a locally advanced rectal cancer, diffuse to the perineum with vein and lymphatic invasion, could metastasize to the penis by different routes.

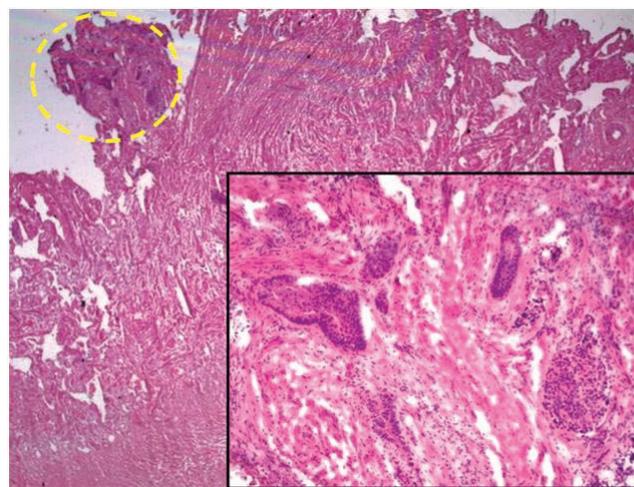


Figure 1. Frozen section of surgical margin (Original magnification 12.5X; insert 200X).

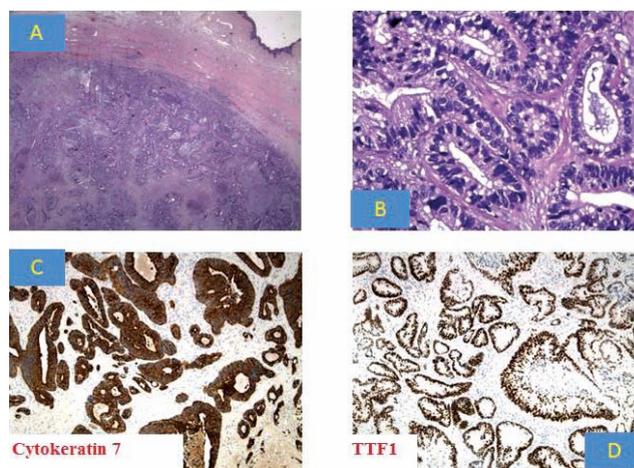


Figure 2. A) Microscopic view of the tumor; B) High-power view showing a proliferation made of gland structures; C) Intense and diffuse cytoplasmic staining for cytokeratin 7; D) Strong and diffuse nuclear staining for TTF1. (Original magnification: A) 12.5X; B) 400X; C) 200X; D) 100).

The most accepted mechanisms of spread are: venous route, lymphatic system, the arterial spread, direct extension (continuity or contiguity) or by iatrogenic implantation.

The venous route, by retrograde flow, is the most common mechanism of spread to the penis. It is considered the major pathway of tumor spread to the penis because of: i) the higher incidence of penile secondary tumors from pelvic tumor by retrograde blood flow; ii) the low incidence of penile secondary malignancy despite the rich arterial inflow; iii) the low incidence of contemporary isolated ilio-inguinal lymph node enlargement in the most frequent causes of penile metastasis (*i.e.* tumor of pelvic organs), except for massive metastases. Anatomically, the blood coming from the cavernous spaces of the penis returns by a series of vessels which converge on the dorsum of the organ to form the deep dorsal vein. Some emerge from the under surface of the corpora cavernosa penis and receiving branches from the corpus cavernosum urethrae ending in the deep dorsal vein, while the largest number pass out at the root of the penis and join the prostatic plexus. The prostatic veins form a well-marked prostatic plexus which communicates with the pudendal and vesical plexuses and with the vertebral vein and hemorrhoidal plexus. The established communication between the dorsal venous system of the penis and the venous plexuses draining the pelvic viscera provide routes for easy transportation of malignant cells from pelvic organs. This route of spread, through complex communication between penile veins and pelvic venous plexus, explains the higher incidence of secondary malignancy by pelvic tumor⁷ since most secondary tumors arise from the prostate, bladder and the recto-sigmoid. The existing connection between the prostatic plexus of Santorini and the deep dorsal vein of the penis are particularly important in prostate and bladder secondary tumors. The retrograde flow also explains the most common localization of the majority of secondary lesions which are located on the corpora cavernosa and the glans of the penis. A frequent contemporary pelvic lymph-node enlargement and compression causing a reversal of retrograde venous flow is sometimes involved, or the presence of an intermittent retrograde flow, for example due to an increase in intra-abdominal pressure.

In advanced recto-sigmoid cancer, there is evidence of extension within the hemorrhoidal veins as a special form of direct local extension. Veins may also be subjected to secondary invasion from neighboring lymphatic metastases.

The mechanism of spread through the retrograde lymphatic route is similar to the venous route. Invasion into the lymphatic system is followed by the transport of tumor cells to regional nodes and ultimately to other parts of the body. Anatomically, the skin of the penis and pre-

puce is drained before the superficial inguinal nodes. The lymphatics of the glans may drain to the superficial inguinal nodes or feed directly to the deep inguinal nodes, while the lymphatics of the corporal bodies may drain to the superficial or deep inguinal nodes. Lymphatics from the lower rectum pass through the perineum into the inguinal nodes and then to the iliac nodes^{8,9} which are the common station of lymphatic drainage. These proximal connections permit tumor cells to spread along these vessels by permeation. This is the most common route of metastasis for carcinomas which spread along these vessels by retrograde permeation.

It is curious that the spread of tumors to the penis through the arterial route is rare, as also are sarcomatous secondary tumors in the penis which usually disseminate through the arterial route. The arterial supply to the penis originates from the right and left internal pudendal arteries which, in turn, arise from the anterior division of the internal iliac arteries and give rise to the common penile arteries. The branches of the common penile artery are: the bulbourethral artery, the dorsal artery of the penis and the cavernosal artery. The bulbourethral artery supplies the penile bulb, the bulbourethral (Cowper) glands, and the posterior aspect of the corpus spongiosum, and it gives rise to the urethral artery. The paired deep dorsal arteries lie external to the tunica albuginea, supplying the penile skin and the glans penis. The deep branch of the penile artery or cavernosal artery enters the cavernous body of the penis and provides the helicine arteries that fill the sinusoidal space. Tumor cells reach, permeate and spread through the arterial circulation by direct tumor extension into the arterial pathways (*e.g.* invading branches of aorta, common iliac, hypogastric or pudendal artery) or metastatic tumor emboli (usually originating from secondary deposits in the lung or other organs which produce metastasis to the lung).

Tumor spread by continuity or contiguity is possible from some closer primary tumors (*i.e.* prostate, bladder, recto-sigmoid) which lie close to the organ. In this case, the metastatic deposit is presumed to be a lesion involving the proximal parts of the penile shaft. This is, strangely, extremely rare.

Tumor spread due to implantation and secondary to instrumentation¹⁰ involves mechanical seeding of tumor cells by surgical instruments. These have been described as possible mechanisms for tumor spread to the penis. This is, however, highly unlikely since isolated lesions of the corpus spongiosum (which surrounds the urethra) without concomitant involvement of other structures, such as the corpora cavernosa or the glans, are extremely rare.

To date, over 500 cases of secondary penile malignancy have been reported.

As primary tumors, bladder cancer,¹¹⁻⁴⁵ prostate carcinoma⁴⁶⁻⁹⁰ and recto-sigmoid cancer⁹¹⁻¹¹⁷ as pelvic malignancy represent about 69% of all cases, followed by renal carcinoma in 6.9%,¹¹⁸⁻¹³¹ hematologic disease,^{132,133} and involvement of lung¹³⁴⁻¹⁵⁹ and other organs.¹⁶⁰⁻¹⁸⁰

The higher incidence of primary malignancy in the pelvic organs means the most common route of tumor spread is through veins and lymphatics and by direct extension; a spread of the tumor in and along prostatic nerves has also been documented.⁴¹ Other primary malignancies, such as lung or kidney cancer, or hematologic disease, usually spread through the arterial route.

These lesions, when synchronous, are often associated with disseminated malignancy and have, therefore, a poor outcome. Sometimes there is metachronous metastatic involvement of the penis only years after the primary tumor has been diagnosed, staged, treated and apparently cured, without evidence of any other metastatic lesions. Most rare is penile involvement as first manifestation of tumor, such as in our case. This seems to be slightly more frequent, at least according to an analysis of the literature, in malignancies secondary to lung cancer.

The mean age of presentation in most cases represents the common age-related incidence of primary malignancy, usually 60-80 years considering the most common primaries, *i.e.* bladder, prostate and rectal

Table 1. List of primary tumours, with cases and incidence.

Primary site	Total number	%
Bladder	144	28.6
Prostate	141	27.9
Rectum-sigmoid	61	12.2
Kidney	35	6.9
Lymphoma-others	34	6.8
Lung	31	6.2
Lower gastrointestinal tract	21	4.2
Upper gastrointestinal tract	11	2.2
Upper airways	4	0.8
Bone	3	0.5
Ureter	3	0.5
Other organs*	16	3.1
Total	504	100

*Other organs included skin, upper gastrointestinal tract, seminal vesicle, stromal tissues, thyroid.

cancer. This represents the common disease-related time between the discovery of primary tumor and the development of metastasis.

About 60% of patients with penile metastasis present with symptoms related to the presence of nodules which in 70% of cases involves both corpora cavernosa. Metastasis is unilateral in only 15% of cases, whereas the corpus spongiosum and glans penis (with skin ulcerative lesions)⁷¹ are each involved in 10% of patients and the prepuce in approximately 5%.^{27,92,99} Exclusive skin lesions are extremely rare according to the most frequent route of dissemination. The high incidence of bilateral involvement is due to the fact that the corpora cavernosa communicate freely through an incomplete midline septum. Mass or induration of the penis is the most common presentation for bladder (89% of cases), prostate (96%) and recto-sigmoid (95%) cancers which usually are solid adenocarcinoma.

Priapism, the so-called malignant priapism,^{11,16,20,24,34,44,46,111,123,150} is reported with varying frequencies of from 20 to 53%. It is usually associated with a mass or induration of the penis. It is a prominent feature in most patients with hematologic secondary malignancy¹³³ or in patients with vein invasion and thrombosis, and it mimics a low flow malignant priapism. It is caused by occlusion of the draining veins and/or is secondary to thrombosis in the cavernosal spaces caused by diffusion and invasion by tumor cells, or by irritation of the neural pathways caused by the metastatic tumor. Most rarely, arterial rupture or fistulae due to tumor invasion may result in secondary high-flow priapism.³³

The other common clinical presentations of penile metastasis are problems in voiding, and penile or perineal pain.

Pain is not an initial symptom in most patients but becomes prominent in advanced disease; pain is partly experienced in the penis and partly in the crura or perineum. It is frequent in cases of malignant priapism or massive infiltration of corpora cavernosa.

Symptoms related to obstructive voiding⁸⁴ and hematuria are very rarely reported^{38,120} since urethral secondary malignancy is rare. However, in locally advanced disease, urethral compression and/or invasion are frequent.

Penile metastasis must be differentiated from some pre-malignant and malignant primitive lesions (such as Bowen's disease, erythroplasia of Queyrat, verrucous carcinoma, squamous cell carcinoma, melanoma and sarcoma), some infective diseases (tuberculosis, chancroid, syphiloma), and other most common benign conditions, mainly Peyronie's disease or non-malignant priapism. According to all reported cases, penile secondary malignancy is rarely a *skin* disease, such as primitive penile cancer or infective diseases, and the appearance of a deep nodule or priapism in older patients with a previous history of cancer must be investigated.

Diagnosis is usually made by biopsy^{15,34} or fine-needle aspiration¹⁸¹ which helps to differentiate between metastasis¹⁸² and primary tumors. Some secondary malignancies are variants of common primary tumor histotypes. For example, prostate cancer usually has primary tumors that are compatible with a diagnosis of ductal adenocarcinoma which is a distinct subtype of prostate carcinoma that commonly involves the prostatic urethra.⁵⁹ Immunohistochemistry^{59,97,98} is an excellent technique for typing tumors by the most common histological marker, such as carcino-embryonic antigen to identify adenocarcinoma, cytokeratins to identify carcinomas (but also expressed in some sarcomas), PSA for prostate cancer,⁵⁹ and some cluster of differentiation for renal cell carcinoma, hematologic disease and lymphoma.

Non-invasive modalities, such as ultrasound scan,^{183,184} color-doppler ultrasonography (helpful for differentiating between high- and low-flow priapism), computerized tomography (CT) and MRI are being increasingly used to diagnose and stage the disease, while invasive cavernosography has been abandoned.^{185,186} However, ultrasonography is operator dependant, whereas the imaging of CT in only one plane limits the diagnostic value of the test. MRI scanning is a reliable alternative for confirming the diagnosis and assessing in detail the exten-

sion of the disease.^{187,188} On T1-weighted images, these lesions usually have low signal intensity, similar to the surrounding corpus cavernosum. On T2-weighted imaging, they appear non-homogenous with low to intermediate signal intensity seen clearly against the high background intensity of the cavernosal bodies.

Metastatic cancer may be treated with systemic therapy (chemotherapy, biological therapy, targeted therapy, hormonal therapy) local therapy (surgery, radiation therapy), or a combination of these treatments.³¹ The choice of treatment generally depends on the type (histology) of the primary cancer, the size, location, and number of metastatic tumors, patient age and general health, and the type of any previous treatment. Even in cases of penile secondary, the choice of treatment is greatly influenced by the general health of the patient, as well as the site of the primary tumor, the extent of metastatic spread, and the severity of systemic and local symptoms. Most older patients will require only supportive or palliative therapy.

Local excision, partial or complete penectomy,^{41,151,189} external beam radiotherapy,¹⁰² brachytherapy⁶⁷ and chemotherapy³⁹ have all yielded poor local results. Standard treatment of priapism is usually ineffective.⁴⁶

Except for a few patients with small isolated lesions which might respond to a wide excision or penectomy, most succumb to the disease process within a year of presentation. For intractable pain, total penectomy or dorsal nerve section may be indicated, while in cases of urethral stenosis, a temporary urinary diversion (*i.e.* supra-pubic catheter⁵⁷) is sufficient. For palliation purposes, the potential benefit of combining radiotherapy and chemosensitizer can only be speculated because of the scarcity of data and clinical experience. Oxygen is a potent radiosensitizer and increases the effectiveness of radiation by forming DNA-damaging free radicals. However, the flaccid penis has a hypoxic cavernosal state which increases in the presence of priapism, and both conditions are typical of penile secondary malignancies. Other radiosensitizing agents, such as cisplatin, 5-fluorouracil, 5-iodo-2'-deoxyuridine, gemcitabine, capecitabine, fludarabine, or imatinib are currently in common clinical use to improve radiation therapy. However, there are few experiences of penile secondary malignancies.

In general, the outcome of patients presenting with secondary malignancy in the penis is very poor. Most patients have widespread metastatic disease. They are in poor general health and will die within six months of presentation, irrespective of the primary tumor and treatment, making palliative non-invasive treatment advisable. Overall, patients with prostate tumor seem to fare slightly better, with survival reported of over nine years.¹⁹⁰ Patients with genitourinary primary (bladder) had an average survival of only 47 weeks, even with aggressive treatment.

Conclusions

Secondary malignancy of the penis is uncommon and clinical evidence of penile involvement in a patient with a history of malignancy is an ominous sign and should alert the clinician to a dismal prognosis.

The rarity of these lesions, the variety of clinical presentation and the overall poor outcome make planning a well-balanced and appropriate treatment after histological diagnosis extremely problematic. This review has also emphasized that in patients with a known primary malignancy, even if cured, the development of penile mass, painful priapism, and lower urinary tract symptoms indicate that, although rare, metastases to the penis should be considered in differential diagnosis and correctly addressed. Most penile secondary malignancies come from prostate, bladder or the recto-sigmoid, and are usually associated with disseminated metastatic disease. Diffusion to the penis is usually by the retrograde venous route, followed by lymphatic and direct invasion.

In the case presented here, penile tumor represented the first clini-

cal manifestation of unknown metastatic lung cancer. This patient had adenocarcinoma of the lung that metastasized to the penis; this has only been reported twice.^{135,150} Arterial spread may be a more plausible explanation for the metastasis from lung cancer, only occurring in the deep corpora cavernosa without involvement of the skin or prepuce, mimicking a diffuse and painful Peyronie's disease.

The overall outcome is very poor and most patients will require only palliative or supportive care. However, in cases of local untractable pain or urethral stricture, partial amputation with urethral clearing will at least improve the quality of life to these patients who have very limited prospects of survival.

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