



Case report

Unusual asymptomatic presentation of bladder cancer metastatic to the penis



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ABSTRACT

Penile metastasis is an extremely rare event and mainly originate from primary pelvic tumor sites such as urinary bladder, gastro-intestinal tract and prostate and more rarely from respiratory system, bone tumors and melanoma. Here we describe the unusual presentation of two bladder urothelial cancer metastatic to the penis with no relevant clinical symptoms. Namely, a 69 years-old man with a warty lesions of the foreskin and the glans misunderstood for a condylomata that at histological and immunohistochemical analysis showed a bladder urothelial carcinoma; and a 71 years-old man with reddish skin lesion of the glans, a previous history of bladder and urethral carcinoma and histological pagetoid spread of urothelial cancer to the glans.

Recurrent bladder urothelial carcinoma is usually a visceral disease that rarely presents as a superficial asymptomatic skin lesion. The two reported cases were asymptomatic superficial penis metastases with a relatively slow growth and a fairly good prognosis after conservative surgical approach. Accurate clinical examination of the penis is mandatory for males with history of bladder cancer.

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1. Introduction

Tumor metastasis to the penis is an extremely rare event despite its rich vascularization and the extensive lymphatic network with the adjacent organs. Most cases of secondary penile malignancy originate from pelvic primary sites and are usually associated with a disseminated disease and a poor prognosis. Up to date there are 504 reported metastatic penile cancers: 70% with primary tumor in the genitourinary tract, 21% in the gastro intestinal tract; 5% in the respiratory system, and the remaining 4% as metastases from primary bone tumors and malignant melanoma [1,2].

A number of mechanisms of metastasis have been suggested including direct tumor extension, retrograde venous, arterial, lymphatic, or iatrogenic spreading [1].

The most common path of tumor dissemination from primary pelvic tumors is through veins and lymphatics or by direct extension. Spreading of the tumor in and along prostatic nerves has also been documented. Other primary malignancies, such as lung or kidney cancer, or hematological tumors, usually follow arterial dissemination [2].

These metastatic lesions are often associated with a primary advanced and aggressive tumor, bearing poor outcome. Usually the involvement of the penis is documented only years after the primary diagnosis [2].

The mean-time between primary tumor and penile metastasis ranges from 3 to 60 months and the time between diagnosis of penile metastasis and death ranges from 0.25 to 18 months [3].

Clinical manifestations of penile metastases include malignant priapism in 20% to 50% of the cases, penile masses or nodules, ulceration, obstructive or irritative urinary symptoms and hematuria [4].

Herein we describe two cases of penile metastases from urinary bladder cancer, the first with a warty-like presentation in the foreskin and the other with a pagetoid spread to the glans.

Abbreviation: BUC, bladder urothelial carcinoma.

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2. Report of cases

2.1. Case 1

A 69-years-old man presented to our Urology Clinics at S. Orsola-Malpighi Hospital (Bologna) with condylomata acuminata of the foreskin and the glans. The patient had no other symptoms and reported a history of recurrent condylomata acuminata since January 2015 treated with topical therapy for 6 months at the Department of Dermatology with no significant response. According to the clinical recurrences the patient underwent surgical excision of the lesion by circumcision.

Macroscopically the lesion was made up of several brownish warty fragments overall 4.5×2 cm and $2 \times 1.5 \times 2$ cm of normal foreskin. Histologically, there was a superficially spreading lesion composed by papillae with fibro-vascular cores. Neoplastic cells had wide cytoplasm, round nuclei and prominent nucleoli. Evidence of squamous-like histological features, nuclear atypia and micro-infiltrative areas were focally present (Fig. 1A and B). No lympho-vascular invasion was seen. At immunohistochemistry, the neoplastic cells were immunoreactive for GATA3, CK7 and CK20 with a focal immunoreactivity for CK14 (Fig. 1C–F). Staining for p16 was negative. The clinical history revealed a previous diagnosis of bladder urothelial carcinoma (BUC), pT2 G3, N0, Mx according to AJCC 2010, 7th edition [5]. The diagnosis of primary multifocal bladder cancer was established in June 2014, after urgent cystoscopy due to recurrent episodes of hematuria. At the time of primary diagnosis of bladder cancer, the clinical examination revealed no lesions of the genitals, and the patients underwent to an abdominal CT scan with contrast medium that revealed no sign of lymphatic or visceral metastasis. The interval between the disease presentation in the bladder and the final diagnosis of penile metastasis was 7 months. According to the clinical history, the results of immunohistochemistry and the non-typical morphological features of penile cancer we decided to perform an HPV genotyping analysis by Reverse Dot Blot PCR that turned out negative, thus confirming the diagnosis of metastatic superficial spreading of bladder cancer to the foreskin.

After the diagnosis the patient underwent to a control cystoscopy that showed a normal urethral wall. In November 2015 the lesion recurred in the glans and was treated with laser therapy conservatively. Until July 2016 the patient was well and free from metastasis.

2.2. Case 2

A 71 years old man presented in 2014 at the Urology Clinics of the Careggi Hospital (Florence) for a routine clinical follow up. The physical examination of the glans revealed a reddish skin lesion that was immediately biopsied. The clinical history of the patient started in July 2004 with several endoscopic diagnosis of high grade BUC pTa/pT1 [5]. In June 2012 he underwent radical cystectomy with a diagnosis of high grade urothelial carcinoma of the bladder (pT1 N0 Mx) of the prostatic urethra (pT2 N0 Mx) and the membranous urethra (pT1, Nx, Mx) [5]. After the occurrence of hematuria the patient underwent in February 2014 a resection of penile urethra. The histological diagnosis confirmed the presence of a high grade papillary urothelial carcinoma with infiltration of corpus spongiosum. The interval between the first diagnosis of bladder cancer (pTa) and the occurrence of penile lesions was 10 years.

The current histological examination of the glans showed large, pale cells arranged in small nests just above the basal layer with a cleft-like separation between the neoplastic cells and the normal epidermal keratinocytes. The cells showed diffuse nuclear atypia and several mitotic features (Fig. 1G).

At immunohistochemistry, the neoplastic cells were reactive for GATA 3 and CK7 and a diagnosis of urothelial carcinoma with

pagetoid infiltration of the glans epithelium was made (Fig. 1H and I).

After this diagnosis the patient underwent a complete resection of the glans and biopsies of corpora cavernosa and negative surgical margins. At the last available follow up on March 2015 the TC scan revealed multiple repetitive hepatic lesion and the enlargement of several abdominal lymph-nodes.

3. Discussion

Penile metastasis from primary bladder cancer is an extremely rare event and represents 30–34% of all metastatic disseminations [6]. Recurrent BUC is usually a visceral disease which rarely presents as a superficial skin lesion [2]. The main clinical manifestations are mass forming lesions with induration and nodules in 51%, priapism in 27%, urinary symptoms like hemorrage, hematuria, incontinence, and irritative and obstructive symptoms in 27%, pain in 17%, retention in 13% and skin lesions in 11% of the patients [7]. We reported two cases of penile metastasis from urothelial cancer with atypical superficial presentation.

The first was characterized just by warty lesions of the foreskin, with no symptoms, that was initially treated as a condilomata acuminata. The histological features of superficial spreading of the cancer cells with no invasive neoplasia are in keeping with the absence of clinical symptoms. Interestingly, the dissemination of the neoplasia to the glans derived from a pT2 N0, G3 BUC with no involvement of the urethral tract and no lympho-vascular invasion in the primary tumor. Without anamnestic information, the problem of the differential diagnosis between primary penile neoplasia and a metastatic disease could rise. In our case we have been aware of the clinical history later and in order to rule out a primary penile neoplasia such us condiloma acuminatum, papillary squamous cell carcinoma, wharty squamous cell carcinoma or mixed wharty-papillary basaloid carcinoma and a metastatic lesion we proceeded with an HPV analysis. The negativity of this test, the negativity for p16 and the positive immunostaining for GATA3 further supported the metastatic origin of the lesion since all the lesions mentioned above are HPV-correlated.

In the literature, the silent presentation of the penile metastases and the superficial skin lesion are described as first symptoms but are not frequent. Therefore, physical examination of the penis of subjects who underwent surgical procedures for bladder cancer should be considered in the follow up of these patients.

The second case reports a pagetoid spreading of BUC after two years from the radical cystectomy and ten years from the first bladder cancer diagnosis. Less than 15 cases of this type of diffusion are described and the most became evident after several years from the radical cystectomy. Only in 1 case the glans paget's disease was diagnosed before the primary urothelial carcinoma of the bladder [8]. These cases were almost all high grade urothelial carcinoma with only 3 cases of low grade urothelial tumors [9] and except for 4 cases that presented an in situ or minimal invasion neoplasia (1 case pTa and 3 cases pT1) all the others were in advanced stage of the disease [8]. In our case the primary tumor was an high grade pT2 neoplasia at cystectomy but presented at the time of first surgery an intraurethral dissemination that in turn lead to an infiltration of the spongiosum and finally to the paget's disease of the glans and metastatic spreading in the follow-up. The main differential diagnoses were: primary penile Paget's disease, squamous cell carcinoma in situ with a pagetoid pattern, superficial spreading of malignant melanoma, penile koilocytosis, pagetoid dyskeratosis, clear-cell papulosis, and mucinous metaplasia. Positive immunostaining for CK7 and GATA3 and negativity for p16 can discriminate primary penile lesions from secondary Paget's disease of a bladder cancer [10].

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