

Case Report

Epithelioid sarcoma of the penis—a rare differential diagnosis of Peyronie’s disease

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We report on a case of penile epithelioid sarcoma in a 29-year-old man presenting with a dorsal penile plaque that primarily was misdiagnosed as Peyronie’s disease. Although the initial clinical findings of these two different entities appear similar, the consequence for the patient is severe. The only way of differentiating these disorders are histological findings. The principal microscopic characteristics of epithelioid sarcoma are the distinctive nodular arrangement, central degeneration and necrosis of the tumor cells with epithelioid appearance and eosinophilia. Immunohistochemical data (cytokeratin, epithelial membrane antigen, vimentin, CD 34, desmin) confirm the diagnosis. We conclude that in cases with slightest doubts on the diagnosis of Peyronie’s disease, especially in younger men suffering from a fast-growing penile induration, a bioptic clarification of the entity should be performed to exclude a high malignant disease that can be only treated as far as it is localized by radical surgery.

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Introduction

Penile epithelioid sarcoma is a rare tumor entity and has been reported in only 18 cases in the literature until now.^{1–18} Typically, patients present with a Peyronie’s plaque-like induration of the penis, local pain, with or without penile curvature, sometimes with dysuria in cases of urethral narrowing and exulceration (Table 1).^{1–18} It mainly affects younger men under 40 years.^{1–3,5–18}

It is a malignant soft tissue tumor of unclear cell type and origin. Morphologically, epithelioid sarcoma is characterized by a mixture of epithelioid and spindle cells, that are often arranged in nodular aggregates around a central necrosis.^{19,20} Three subtypes of epithelioid sarcoma have been described:²⁰ The fibroma-like variant is characterized by a collagen-rich storiform pattern. The angioectoid or angiomatoid variant shows a pseudovascular growth pattern due to cystification and abundant

intralesional hemorrhage. A solid pattern with large, rhabdoid-appearing cells is typical for the large cell, rhabdoid, or proximal variant.²⁰ Histogenetical and immunohistochemical studies discuss relations to fibroblasts, histiocytes, synovial cells, primitive mesoderm-related stem cells, and neuronal cells.²⁰ Since its first description, epithelioid sarcoma has been found to occur in the extremities, the trunk, the scalp, the vulva, and the penis, respectively.^{1–20}

The recommended treatment is a wide resection with adequate margins, lymph node dissection, and optional adjuvant radiotherapy.²⁰ The best therapeutic results (Table 1) have been achieved after total or subtotal penectomy, with or without adjuvant radiation therapy.^{4,7,9,10,12,13,17,18} Prognostic data are unprecise concerning the very short follow-ups of up to 24 months,^{1–7,9,10,12–18} there have been only two observations up to 8 and 10 years, respectively.^{8,11} There is a tendency for a better prognosis after excision, but since the follow-up periods in all cases are too short with regard to the formation of metastases,⁸ a real prognostic statement appears to be impossible at present.

Due to its clinical similarity, it is obvious that the most important clinical differential diagnosis of penile epithelioid sarcoma is Peyronie’s disease.^{2,9,10,12,16–18} Other misdiagnoses were urethral stricture,⁴ infection of the glans penis.⁶ In two other cases, penile epithelioid sarcoma was primarily

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Table 1 Previous reported cases of penile epithelioid sarcoma

Reference	Patient age (y)	Symptom duration	Symptoms and presentation	First diagnosis	Therapy	Course (duration of follow-up)
Dehner and Smith ¹	35	12 y	Nontender mass, urethral compression	Fascial sarcoma	Excision	Lost to follow-up
Moore <i>et al</i> ²	23	6 y	Nontender mass, pain, curvature	Peyronie's disease	Partial penectomy, chemotherapy, radiation	Metastases to lung, kidney, skin (18 months)
Iossifides <i>et al</i> ³	31	1 month	Mass, dysuria	Urinary infection	Partial penectomy	No evidence of disease (6 months)
Zungri <i>et al</i> ⁴	43	3 y	Urethral stenosis	Urethral stricture	Total penectomy	No evidence of disease (12 months)
Pueblitz <i>et al</i> ⁵	32	2.5 y	Mass, dysuria, dyspareunia, urethral compression	Granulomatous inflammation	Total penectomy, radiation	Metastases to lung and scalp, but no local recurrence, (15 months)
Gower <i>et al</i> ⁶	39	3 months	Painful mass on glans penis, dysuria	Infection	None	Continued local spread (2 months)
Leviav <i>et al</i> ⁷	26	6 months	Mass, ulceration, urethral compression	Fibroxanthoma	Partial penectomy, plastical reconstruction	No evidence of disease (12 months)
Millan <i>et al</i> ⁸	32	10 y	Nontender mass	—	Total penectomy	Skin metastasis (10 years)
Huang <i>et al</i> ⁹	26	10 y	Mass, erectile pain and deviation, urethral compression	Peyronie's disease	Total penectomy, radiation	No evidence of disease (24 months)
Dominguez <i>et al</i> ¹⁰	43	3 months	Fibrous plaque without curvature	Peyronie's disease	Total penectomy	No evidence of disease (24 months)
Guillou <i>et al</i> ¹¹	39	3 months	Nodules, swelling, dysuria	—	Radiation	Local recurrence (2 months), no evidence of disease (8 y)
Corsi <i>et al</i> ¹²	34	3 y	Firm plaque, penile deviation, pain during erection, urinary retention	Peyronie's disease	Total penectomy	No evidence of disease (22 months)
Sarica <i>et al</i> ¹³	36	—	Pain and tenderness in the perianal region, resulting from unusual palpable mass	Tumor of the corpora cavernosa	Total excision, radiotherapy	No evidence of disease (13 months)
Yaman <i>et al</i> ¹⁴	38	24 months	Nodular penile mass at perineum, erectile pain	First varicocele, later prostatitis	Partial penectomy	Local recurrence (6 months)
Sirikci <i>et al</i> ¹⁵	38	6 months	Firm, painless slowly growing nodule	Tumor of the corpora cavernosa	Biopsy, refused further therapy	—
Oto and Meyer ¹⁶	39	—	Dorsal fibrous plaque, penile deviation	Peyronie's disease	Total penectomy	—
Orsmy <i>et al</i> ¹⁷	39	13 y	Painful penile nodule	Peyronie's disease	Total penectomy	No evidence of disease (6 months)
Rossi <i>et al</i> ¹⁸	35	10 months	Penile deviation, erectile dysfunction, urethral stenosis, painful penile nodule	Peyronie's disease	Total penectomy	No evidence of disease (20 months)
Own case	29	9 months	Painless rigidity of penis	Peyronie's disease	Chemotherapy	Multiple metastases to lung, spine and lymph nodes (18 months), dead (24 months)

misdiagnosed histologically as granulomatous inflammation or and fibroxanthoma.^{5,7}

Case report

A 29-year-old man presented with a dorsal penile plaque formation lasting over 5 months diagnosed as Peyronie's disease. He was treated with potassium-

para-aminobenzoate (PotabaTM) over 3 months. Since a severe enlargement of the plaque was observed, which was interpreted as progression of Peyronie's disease, he finally was referred to our department. At this time, the corpora cavernosa were palpable hard overall the total penile length and without unifocal plaque formation. Sonographic examination demonstrated a slight hyperdensity in both corpora cavernosa. With doubts on the initial diagnosis of Peyronie's disease, biopsies

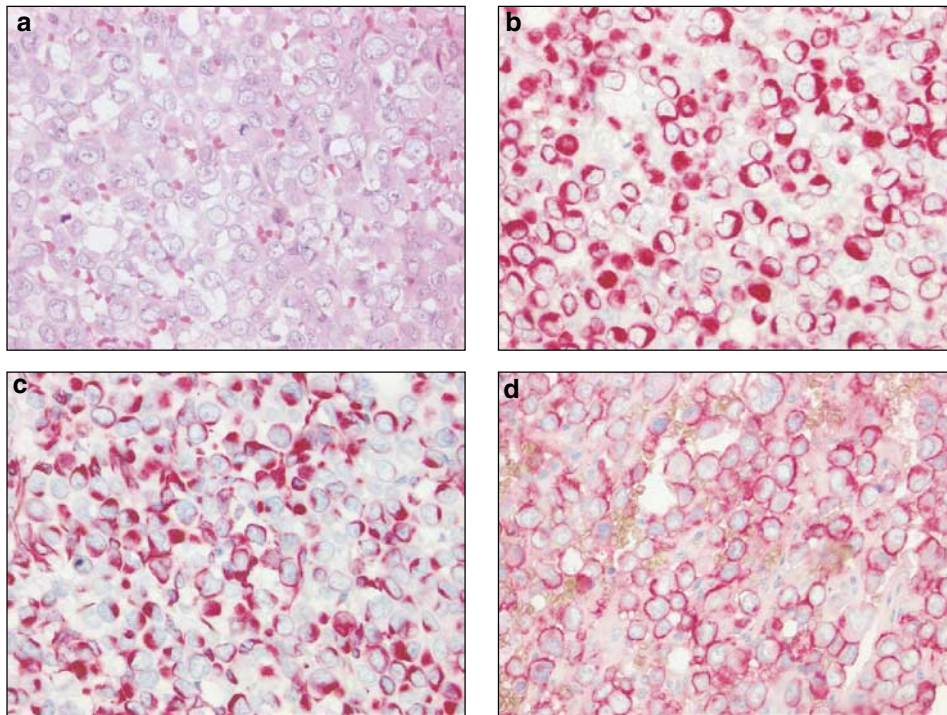


Figure 1 (a–d) (original magnification $\times 400$): (a) Typical morphologic and immunohistochemical features of penile epithelioid sarcoma with sheets of epithelioid tumor cells separated by extravasated erythrocytes (hematoxylin and eosin). The principal microscopic characteristics are the distinctive nodular arrangement of the tumor cells, their tendency to undergo central degeneration and necrosis, and their epithelioid appearance and eosinophilia. The constituent cellular elements range from large ovoid or polygonal cells with a deeply eosinophilic cytoplasm to plump spindle-shaped cells. (b) Intracytoplasmic tumor cell staining for vimentin antibody V9 and (c) cytokeratin antibody MNF 116. (d) The tumor cells have a weak intracytoplasmic staining for CD34.

of the corpora cavernosa and the adjacent tunica albuginea were taken under the suspicion of a malignant disease.

The surface of the surgical specimen appeared grayish-white, granular, and hard. The histological examination showed focal, highly proliferative undifferentiated malignant cells within fibrotic tissue of the corpus cavernosum. The polymorphic hyperchromatic tumor cells with eosinophilic cytoplasm showed a distinctive nodular arrangement with central degeneration and necrosis (Figure 1a–d). The nuclei were large, pleomorphic, and marginal. Focally, rhabdoid structures were evident. Furthermore, spindle-shaped cells with small, hyperchromatic nuclei occurred. The mitotic count of three to five mitosis per 10 high power fields (hpf) was increased and the surgical resection margins were infiltrated by the tumor. Intracytoplasmic hyaline inclusions were not seen. Immunohistochemical findings are shown in Figure 1b–d. Neoplastic cells were immunoreactive for cytokeratin (MNF 116), epithelial membrane antigen (EMA), vimentin (V9), CD 34, and desmin (D33). The reactions with the other antibodies used in this case were negative: SMA (1A4), chromogranin A, synaptophysin, NSE, BMA 120, ACE (CG II), CD 31, CD 68 (KP-1), HMB 45, and S-100. The initial diagnosis of Peyronie's disease clearly could be ruled out histologically. The diagnosis was epithelioid sarcoma of the proximal

type with the less probable alternative of being an extrarenal rhabdomyoid tumor.

Spreading of tumor was evaluated by computer-tomography (CT) and magnetic resonance imaging (MRI) (Figure 2). The tumor seemed to originate from the right corpus cavernosum infiltrating wide parts of the pelvis, the urethra, the prostate, the right ischiadic tuber, and the right proximal adductor muscles. On T1-weighted MR images, the tumor was shown with a low signal, lower than the surrounding muscles (Figure 2). The general tumor staging included whole-body CT, MRI of the pelvis and abdomen, bone scintigraphy, gastroscopy, and colonoscopy, in order to exclude the possibility of a distant primary tumor or metastases.

The patient refused radical surgery proposed as complete pelvic exenteration and demasculinization with continent urinary bowel diversion and terminal stoma of the sigma. After interdisciplinary consultation, a chemotherapy trial was initiated with the VAIA scheme (Vincristin, actinomycin D, ifosfamide, and adriamycin). At the time of re-evaluation, the MRI showed progressive disease in the pelvis, in some areas without contrast enhancement, interpreted as a partially necrotized tumor. Due to these findings, the therapy was changed to carboplatin and etoposide. The restaging MRT on day 40 indicated no change. Taking into account the fact that the tumor was sensitive to chemotherapy,



Figure 2 MRI: T1-weighted unenhanced spin echo image of pelvic floor at the level of the ischiadic tuber showing the tumor with low signal. The signal is a little lower than the surrounding muscles. The right corpus cavernosum is infiltrated, causing a bowing to the infiltrated right side. The tumor invades the right ischiadic tuber and right proximal adductor muscles.

dose escalation with high-dose chemotherapy was considered to be an appropriate salvage therapy. Therefore, ifosfamide was used with 2 g/m²/day on days 1–7 with G-CSF support and one repetition on day 30. This procedure was subjectively tolerated very well, but restaging showed further progression of the disease. The patient was referred for radiation therapy of 40 Gy on the pelvic tumor, but nevertheless developed pulmonary and osteolytic metastases. A metastasis in the first lumbar vertebra was stabilized 21 months after the onset of the disease. At 2 years after the initial symptoms of the disease, the patient died due to progressive tumor spread.

Discussion

In cases of penile induration, Peyronie's disease is usually supposed to be the diagnosis deduced from the clinical aspect as it was described by several authors^{2,9,10,12,16–18} and as has happened in our case, although penile epithelioid sarcoma is the cause of these symptoms. In contrast to the rare occurrence of epithelioid sarcoma, Peyronie's disease is much more common with an incidence of up to 3.2%.²¹ Thus, although very rare, epithelioid sarcoma has to be taken into consideration as a differential diagnosis of Peyronie's disease, because the consequence for the patient is severe. Peyronie's disease is a benign disease, whereas a high malignant process that can be only cured before generalization by radical surgery is a possible diagnosis.

How can it be differentiated between these two diagnoses? Imaging procedures cannot clearly differentiate between Peyronie's disease and epithe-

lioid sarcoma, but can provide hints for a malignant process: in contrast to Peyronie's disease that usually is localized at the tunica albuginea, epithelioid sarcoma show infiltrating lesions of the corpora cavernosa.^{16–18} In our case, ultrasound did not provide any clear diagnostic hint. On MRI, besides thickening of tunica albuginea as typical for Peyronie's disease, infiltration of the corpus cavernosum with low signal on T1-weighted images, strong inhomogeneous enhancing tumor after application of contrast medium and inhomogeneous, high signal intensity, cystic like on T2-weighted images were also described. CT scan visualized an infiltration of the corpus cavernosum, and the surrounding tissue of ischiadic tuber and the proximal adductor muscles. Unfortunately, only in seven^{12–18} of 18 reported cases of penile epithelioid sarcoma data on local findings on ultrasound^{14,15} or MRI,^{12–18} but never on CT are provided. By ultrasound, epithelioid sarcoma was described as a solid mass lesion of the corpora cavernosa with local calcifications.¹⁵ On MRI, epithelioid sarcoma was evident as an infiltrating lesion of the corpora cavernosa.^{12–18} While T2-weighted images demonstrate an irregular area of low signal intensity and nodules of central high signal intensity, the area was isodense to normal tissue on T1 weightings.^{15–17} In summary the data on imaging of epithelioid sarcoma are poor. Due to the lacking knowledge on large series of imaging in these patients, we believe that an epithelioid sarcoma cannot be excluded by imaging procedures only. We deduce from this experience that in any kind of doubt on the clinical diagnosis of Peyronie's disease, a penile biopsy should be taken. Learning from this case in which we performed surgical biopsy, we introduced a simple technique of percutaneous punch biopsy of the tunica albuginea using punch biopsy gun ('Manan Pro-Mag 1.2', Medical Device Technologies Inc., Gainesville, USA) with a 14-gauge biopsy needle ('Manan SACN 14 ga × 8 cm', Medical Device Technologies Inc., Gainesville, USA). To our mind, there are at least two indications for penile punch biopsy in doubts on the initial diagnosis of Peyronie's disease. First, a fast increasing size of the induration could be a hint that the process is malignant. Second, penile induration in young patients is suspect for malignancy, because Peyronie's disease usually occurs during the fifth and sixth decade of life, although an occurrence in younger patients has been described in rare cases.²¹ The young age is a very important aspect as epithelioid sarcoma occurred mostly in men under 40 years.^{1–3,5–18}

However, also the pathological differential diagnosis is also difficult and includes especially the extrarenal malignant rhabdoid tumor.^{22,23} The principal microscopic characteristics of epithelioid sarcoma are the distinctive nodular arrangement of the tumor cells, their tendency to undergo central degeneration and necrosis, and their epithelioid appearance and eosinophilia. The constituent

cellular elements range from large ovoid or polygonal cells with deeply eosinophilic cytoplasm to plump spindle-shaped cells. Large pleomorphic nuclei with small or prominent nucleoli and a mitotic count of >5 mitosis per 10 hpf are characteristic. Binucleated or multinucleated tumor cells were occasionally observed. Distinctive loss of cellular adhesion with secondary hemorrhage and focally prominent intercellular deposition of dense hyalinized collagen were also observed. Differential diagnoses include mainly conventional epithelioid sarcoma,¹⁷ extrarenal malignant rhabdoid tumor, epithelioid malignant peripheral nerve sheath tumor, melanoma, rhabdomyosarcoma, and undifferentiated carcinoma with rhabdoid features. Epithelioid malignant peripheral nerve sheath tumors and melanoma are easily discarded by S-100 protein and HMB 45-negative reactivity and strong cytokeratin and EMA positivity. Epithelioid or rhabdoid rhabdomyosarcoma show a strong and diffuse reactivity with muscle markers, but lack epithelial markers, including EMA. The presence of CD 34 reactivity is the single finding, except the lack of previous history of primary or metastatic carcinoma, that would support a diagnosis of epithelioid sarcoma, because carcinomas are—in their great majority—CD 34 negative lesions.²⁴ Extrarenal rhabdoid tumor seems to be most common in infants, but may also affect adolescents and adults. Microscopically, extrarenal rhabdoid tumor is defined by round or polygonal cells with vesicular nuclei, prominent nucleoli and abundant cytoplasm containing acidophilic and PAS-positive hyaline inclusions or globules.^{22,23} The tumor cells show a positive immunoreactivity with antibodies against cytokeratin, EMA and vimentin, and the absence of demonstrable immunoreactive desmin and myoglobin.^{12,17} To date, the evidence is strong enough to suppose that, at least in extrarenal locations, rhabdoid tumors are not a distinctive entity but rather represent the shared morphologic pattern of a diverse range of malignant neoplasm.^{22,23} Assuming that extrarenal rhabdoid tumors do not correspond to a well-defined entity and that the distinction between epithelioid sarcoma and extrarenal rhabdoid tumor may be somewhat arbitrary, we conclude that the morphologic and immunohistochemical features of the tumor described herein fits with a large cell variant of epithelioid sarcoma.

In contrast to the clinical appearance, the histological differential diagnosis of Peyronie's disease is simple. The main pathological finding in Peyronie's disease is the marked fibrosis of the tunica albuginea, not the corpora cavernosa.²¹ In early stages, fibroblastic proliferation and perivascular infiltration of lymphocytes of the tunica albuginea are characteristic. Later on, there is marked fibrosis and collagenization; calcification and ossification may finally occur in the fibrous plaques.²¹

In conclusion, in any case if doubts arise on the diagnosis of Peyronie's disease—this can be a fast

increasing penile induration or the young age of the affected patient—penile biopsy should be performed early to exclude a high malignant disease that can only be treated as far as it is localized by radical surgery.

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