Case Report

Primary epithelioid hemangioendothelioma of the penis: a case report and literature review

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Abstract: Epithelioid hemangioendothelioma (EHE) is a rare vascular tumour with an intermediate behaviour between benign hemangioma and malignant angiosarcoma. There is scarce data on the penile EHE's management and its natural history, as our knowledge is based on few reported cases with a short follow-up period. We present a case report and conducted a literature review, including 17 cases. The relevance of this case report derives from the need for better clinical characterization of patients with penile EHE and the importance of defining the outcomes. We report the case of a 53-year-old male with a 1-year history of sleep-related painful erections. Imaging techniques showed a well-defined hypoechoic and hypervascular solid nodule on the dorsal aspect of the penis. It was surgically removed, and the histopathological study revealed a low-risk EHE of the penis. Follow-up magnetic resonance imaging (MRI) and computed tomography did not demonstrate local recurrence nor metastases. According to the literature review, most of the patients were in their fifth and sixth decades of life at the time of diagnosis and lesions were usually located in the glans. The most common clinical presentation was as a painful mass. Follow-up period ranged from 2 months to 5 years. Three patients showed systemic metastases, two of which died due to cancer. The conclusions from the literature review are limited by the reduced number of cases and the short follow-up. This case report highlights the importance of understanding the diagnosis and treatment of this type of rare non-squamous malignant tumours of the penis. Penile EHE is a malignant vascular tumour that is very rare in this location. The best treatment is local excision, with re-excision or intraoperative margins assessment. Occasionally, systemic chemotherapy and radiation therapy can be useful. There is consensus on the importance of very strict follow-up of these patients.

Keywords: Epithelioid hemangioendothelioma (EHE); penile neoplasms; penis; penile cancer; case report

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Introduction

Epithelioid vascular tumours are rare vascular neoplasms. They are a subtype of mesenchymal tumours, defined by their epithelioid morphology, which differentiates them from other vascular tumours (1). Epithelioid hemangioendothelioma (EHE) is an uncommon vascular tumour that was first described in 1975 by Dail and Liebow in the lung as an aggressive bronchoalveolar cell carcinoma (2). EHE demonstrates an intermediate behaviour between benign hemangioma and malignant angiosarcoma. It can occur in soft tissues, bones and visceral organs, but also as a primary tumour of the blood vessels.

Non-squamous cell carcinoma primary malignancies represent fewer than 5% of penile cancers. Soft tissue malignancies of the penis are mainly vascular tumours, such as Kaposi sarcoma, EHE and angiosarcoma, followed by other sarcomas like rhabdomyosarcoma and

leiomyosarcoma (3).

There is a scarcity of published data on penile EHE's management and its natural history. Until 2015, 17 cases of penile EHE have been reported in the literature (4). Of these cases, two presented with metastasis and two with multifocal penile EHE lesions. Furthermore, the benign type of the spectrum, the penile epithelioid hemangioma (EH), is also a very rare vascular neoplasm. Until 2015, only 28 cases in the literature have been reported (5).

To date, reported characteristics of EHE are based on this small number of published cases. The rates of local recurrences, metastases and mortality of this tumour are 10%, 20–30% and 15%, respectively. Treatment decisions should be based on pathological findings. Treatment options include excision or multimodal therapy (1).

We reported the case of an EHE involving the penis in a 53-year-old male treated with complete resection. This case report contributes to widen our knowledge of this rare tumour and the literature review offers an update on its management.

Literature review

We carried out a literature review in PubMed (MEDLINE) of reported cases and analysed therapeutic arsenal (surgery, antitumour drugs and radiation) used in the treatment of these unusual tumours.

The search strategy was as follows: ("Hemangioendothelioma, Epithelioid"[Mesh] OR "Hemangioendothelioma"[Title/abstract]) AND ("Penis"[Mesh] OR "penile"[title/abstract] OR "Penile Neoplasms"[Mesh]). Inclusion criteria were: histologically confirmed cases of penile EHE, and no language or temporal restrictions were applied. Two authors independently reviewed the literature and decided which case reports to include in this study. We summarized the case reports in *Table 1*, and we extracted the most important aspects: age, clinical presentation, size and location, management, follow-up period, local recurrence or metastases, and survival time.

We present the following case in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/tau-21-277).

Case presentation

A 53-year-old patient with a past medical history of hypertension presented to the urology department for penile pain during erections. He denied any penile injury or trauma. He complained of sleep-related painful erections causing sleep disruption that affected his quality of life. He was also experiencing lump sensation and progressive curvature of the penis for one year. Previously, a consultant urologist had diagnosed acute phase of Peyronie's disease. On physical examination there was a dorsal nodule at the root of the penis of 1 cm in size, that was not clearly arising from or depending on the tunica albuginea.

A penile colour Doppler ultrasonography was performed, and it showed a hypervascular nodule in the dorsal aspect of the cavernous body, lateralized to the right, without calcifications, measuring 13×4×3 mm (*Figure 1A*,*1B*). The magnetic resonance imaging (MRI) demonstrated a nodule on the dorsal aspect of the penis (*Figure 1C*).

As penile neoplastic lesion was suspected based on clinical and radiological findings, the lesion was surgically removed with 5-mm surgical excision margins. The lesion was firmly attached to the penile dorsal nerve. Because this is the sensory nerve for the glans and penis, a careful dissection technique was performed in order to avoid nerve injury. Furthermore, we tried to minimize the use of bipolar cautery to avoid nerve trauma.

Gross examination of the specimen revealed a soft tissue mass, measuring 2 cm in its greater dimension. On microscopic examination, although focally surrounded by a thin membrane, the tumour showed an infiltrative pattern, with a small focus of necrosis. It was formed by a densely cellular neoplastic proliferation, with cells arranged in cords at the periphery of the lesion and solid areas in the centre, where we found the remains of a vessel wall (*Figure 2A-2C*). The cells had an epithelioid appearance, with large eosinophilic cytoplasm and frequent intracytoplasmic vacuoles, some of them containing red blood cells. The nuclei were ovoid and vesicular, with variable size and occasional prominent nucleoli and atypia. It was accompanied by a mild intratumoral inflammatory infiltrate, with lymphocytes and eosinophils. Mitotic activity was up to 2 mitoses per 10 high-power fields.

The immunohistochemistry showed intense membrane positivity for CD31 (*Figure 2D*) and nuclear positivity for FLI-1 and ERG. It had a patchy expression of CKAE1-AE3. The tumour was negative against S100, HMB45, MELAN-A and D2-40. Smooth muscle actin highlighted the muscle remains in the centre of the lesion, which could represent a vessel wall. The proliferation index (Ki67) was 7%.

The histopathological analysis revealed a low-risk EHE

Table 1 Case reports of EHE of the penis

Case (author and year of publication)	Age of the patient	Clinical presentation	Size (cm) and location	Management	Low or high risk (published in 2008, Deyrup *et al.*)	Follow-up period (years)	Local recurrence or metastases	Survival time
Zhang *et al.* 2015 (6)	62 yo	Penile mass with pain	4 cm Root of the penis	Phallectomy	Not available	2 months	Not available	2 months
Yoshi-Hiro *et al.* 2015 (7)	43 yo	Painful nodules	Three nodules with a few millimeters in diameter	Not available	Not available	Not available	Not available	Not available
Darshan *et al.* 2014 (8)	59 yo	A painful, enlarging lump on the base of his penis for 5 months The patient was misdiagnosed with penile vein thrombosis versus atypical Peyronie's disease	A 1.25 cm × 0.3 cm vascular mass superficial to the tunica of the dorsal penis	Complete resection	Low-risk EHE	9 months	MRI of the pelvis at 3 months and 9 months did not demonstrate recurrent or metastatic disease	At least 9 months
Abdalla *et al.* 2013 (9)	1 mo	Swelling at the tip of the penis and burning micturition	A fungating 6 by 8 cm mass At the distal part of the penis	Amputation and reconstruction of the penis	Low-grade EHE	Not available	Not available	Not available
Carballo *et al.* 2012 (10)	63 yo	1 cm-size nodule, painful, bluish, located in the glans	1 cm Glans	The new lesion was surgically removed with intraoperative margins assessment	Not available	6 months	Free	At least 6 months
Shin *et al.* 2010 (11)	28 yo	Asymptomatic subdermal glanular lesion	Not available	Partial penectomy	Not available	Not available	Not available	Not available
Wedmid *et al.* 2009 (1)	48 yo	Several violaceous, indurated, subcutaneous lesions	A 1.5 cm plaque-like lesion Located deep within the corporal body near the distal shaft	A multimodal approach (systemic chemotherapy with eight cycles of liposomal doxorubicin + adjuvant radiation therapy)	High risk EFE	18 months	Free of any evidence of local or metastatic progression	At least 18 months
Zastrow *et al.* 2008 (12)	58 yo	Indolent nodule 7 mm in diameter	7 mm On the ventral aspect of the glans penis	Local excision of the tumour Two weeks later we performed a second excision of the remaining tumour	Not available	52 months	Not available	Not available
Gharajeh *et al.* 2006 (13)	42 yo	Small, painful mass of the left dorsal penile shaft, particularly severe with erection (it was confused with penile vein thrombosis)	Two superficial subcutaneous masses that measured 3.6 mm and 10.7 mm in diameter	An excisional biopsy of the penile masses The patient underwent local re-excision of the surgical bed	Low-risk EHE	1 year	No evidence of local or metastatic disease recurrence	At least 1 year
Wen *et al.* 2004 (14)	58 yo	6-month history of penile pruritus associated with a painful progressive firmness (the patient was misdiagnosed with Peyronie's disease)	A 2-cm necrotic ulcer was also noted on the glans penis	Because the metastatic workup revealed hepatic and pulmonary lesions, penectomy was not performed and the patient was treated with paclitaxel	Not available	13 months	He died of progressive tumour spread	13 months
Kamat *et al.* 2004 (15)	46 yo	Skin nodules developed in the subcutaneous lymphatics of the penis as well as the groin	1 to 2 cm node Medial to the right femoral vessels	Resection of the nodules and inguinal nodes in the left groin, and *en bloc* resection of the skin and subcutaneous tissue of the penis and upper scrotum Interferon-3 times weekly for 1 year	Not available	65 months	No evidence of recurrent disease	At least 65 months
Gutiérrez-García *et al.* 2004 (16)	64 yo	Painful erections for 6 months	1 cm Dorsal aspect of penis	Local excision of the tumour with a cut-off of normal tissue	Low risk	1 year	Free	At least one year
Haidar *et al.* 1995 (17)	60 yo	A nodular swelling of the penile shaft of unknown duration	Nodular mass measuring 7x6x3 mm	A complete excision with adequate margins	Not available	Not available	Not available	Not available
Elhosseiny *et al.* 1986 (18)	60 yo	A painless mass of one-year duration	A firm 2.5 by 2-cm nodule over the midportion of the dorsal aspect of the shaft of the penis	Removal by simple excision with a 0.5 cm cuff of fibroconnective tissue	Not available	Not available	Not available	Not available
Deutsch *et al.* 1973 (19)	17 yo	A mass in the left scrotum on a routine physical examination	5x3.5x1 cm It was involving the corpora cavernosa and attached to the urethra	Excision and postoperative irradiation to the primary site. Systemic chemotherapy and radiotherapy to the thoracic spine was administered in the belief that the patient had bone metastases	Not available	5 years	Distant metastases in three different organ systems: pulmonary, osseous, and spinal cord	Not available
Barnett *et al.* 1960 (20)	41 yo	Perineal pain	An ill-defined mass was felt on rectal examination lateral to and proximal to the prostate gland and attached to the ischium	*En bloc* removal	Not available	6 months	No evidence of recurrence or metastases	At least 6 months
Varney *et al.* 1955 (21)	54 yo	A 3-day history of painless hematuria	1 cm in diameter, in the floor of the anterior urethra approximately 6 cm proximal to the urethral meatus	Excision with the resectoscope loop After that, irradiation therapy to the left ischium	Not available	2 years	Ischium lesion	At least 2 years

EHE, epithelioid hemangioendothelioma. yo, years old; mo, month old.

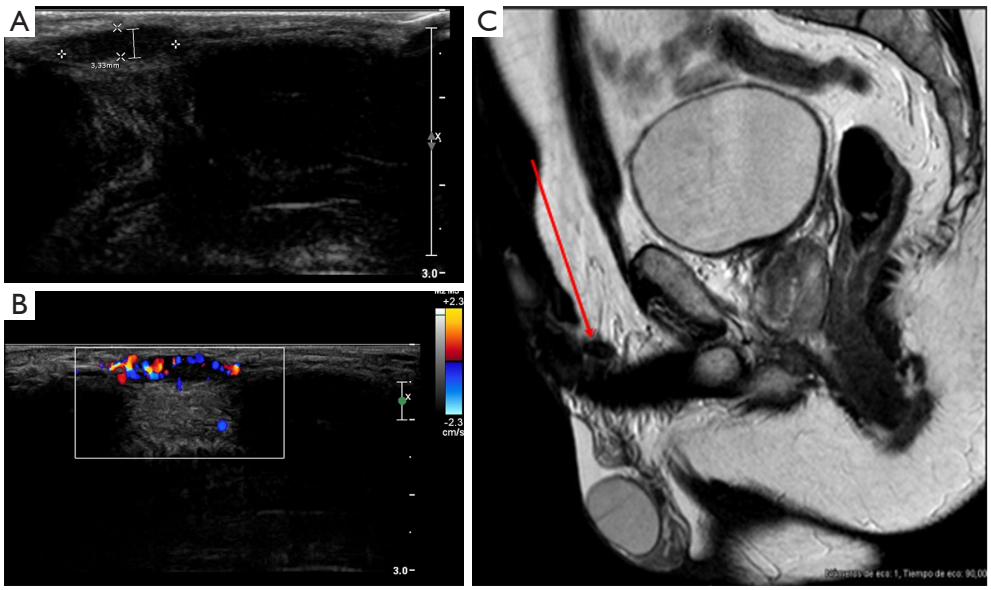

Figure 1 Diagnostic imaging findings on presentation. (A) A transverse ultrasound scan of the dorsal aspect of the midshaft of the penis shows the two paired corpora cavernosa a well-defined hypoechoic solid nodule, located centrally. (B) Doppler images show a hypervascular hypoechoic mass. (C) MRI T2 sagittal, revealing a small nodule (red arrow) in a corpus cavernosum, on the dorsal aspect of the penis.

of the penis. Subsequent penile MRI did not detect local recurrence two and six months after complete resection.

The staging computed tomography (CT) scan was negative for metastatic disease. This case was presented in the uro-oncologic multidisciplinary team meeting and a strict surveillance protocol was chosen.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

Discussion

The term "*epithelioid hemangioendothelioma*" was introduced in 1982 by Weiss and Enzinger to describe a vascular tumour of bone and soft tissue showing features between hemangioma and angiosarcoma (16). EHE was re-classified from the benign tumour (WHO 2007) to a malignant one (2016). The estimated prevalence of EHE is less than one in 1 million (2).

There is very little evidence for the management of penile EHE, because it is based on few individual case reports, with a short follow-up period.

The literature review revealed seventeen cases. Patient age range was one month old to 64 years, but most of the patients were in their fifth and sixth decades of life at time of diagnosis. The size of the lesion was variable, ranging from 0.7 to 6 cm, and most of them were located in the glans. The most common clinical presentation was as a painful mass. Local excision of the tumour (± re-excision) was the most frequent treatment. Three patients needed adjuvant radiation therapy (RT) and five needed systemic chemotherapy (paclitaxel, doxorubicin or interferon). Immunohistochemically, 8 cases were tested and positive for at least one endothelial marker (CD31, CD34, factor VIII). Follow-up period ranges from 2 months to 5 years. Three cases showed systemic metastases and of them, two patients died due to cancer. We present the case of an EHE in a patient in the fifth decade of life, with a size of 13mm and debuting with painful erections.

Patel *et al.* (8), Gharajeh *et al.* (13) and Wen *et al.* (14) published examples of EHE mimicking Peyronie's disease, penile thrombophlebitis or priapism. Otherwise, Zhang *et al.* (6) published the case of a primary pulmonary EHE with penile metastases. Kamat *et al.* (15) reported a case

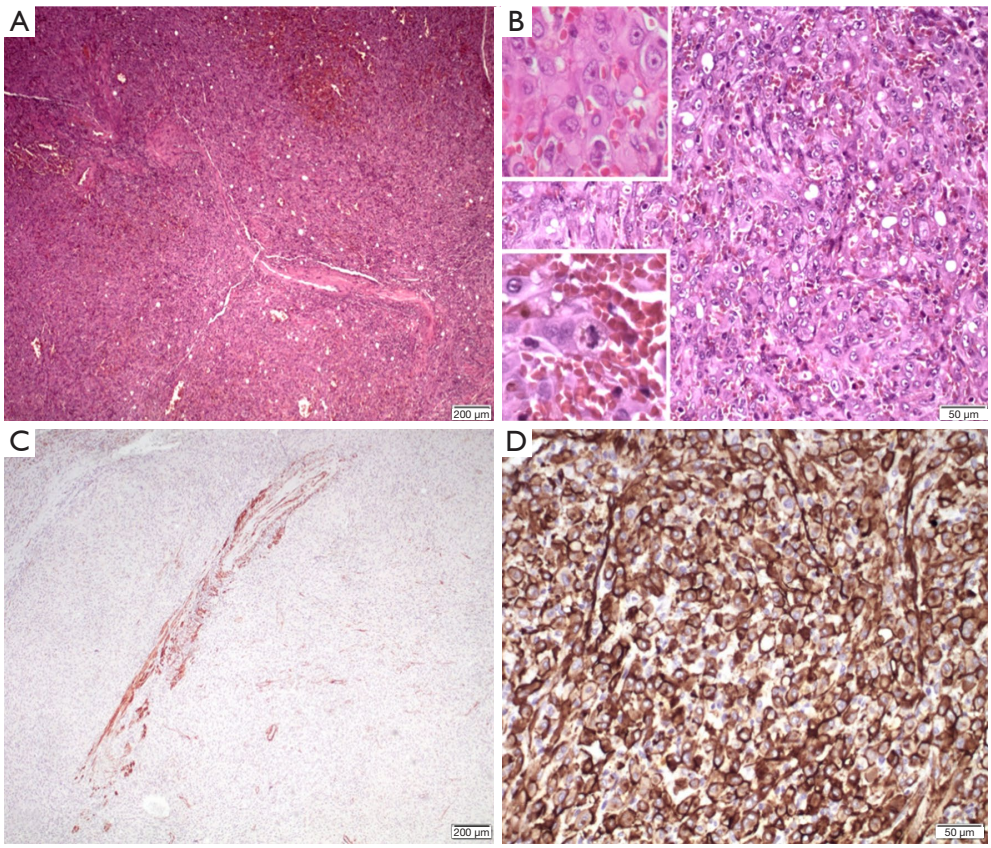

Figure 2 Pathology of the tumour. (A) Haematoxylin eosin (scale bar =200 µm). The tumour is composed of a highly cellular neoplastic proliferation with cells arranged in solid areas. In the centre of the image there are the remains of a vessel wall. (B) Haematoxylin eosin (scale bar =50 µm). The tumour cells have an epithelioid appearance, with eosinophilic cytoplasm, oval nuclei and prominent nucleoli. There are intracytoplasmic vacuoles, some of them containing red blood cells (upper inset). We found up to 2 mitoses in 10 high power fields (lower inset). (C) Smooth muscle actin antibody staining (scale bar =200 µm). There are smooth muscle fibbers in the middle of the lesion, which may represent a vessel wall. (D) CD31 antibody staining (scale bar =50 µm). Diffuse membrane positivity on tumour cell.

of metastatic EHE successfully treated with primary resection and systemic chemotherapy with interferon alpha. Furthermore, Zastrow *et al.* (12) presented a case of recurrent multifocal penis EHE.

EHE of the penis should be considered in the differential diagnosis of patients presenting with painful penile lumps. In addition, it can be misdiagnosed with as Peyronie's disease or penile thrombophlebitis. A thorough histological and immunohistochemical examination is necessary to make the diagnosis. The differential histopathological diagnosis of EHE includes EH and epithelioid angiosarcoma (13). In our case, the patient was initially misdiagnosed with the acute phase of Peyronie's disease, as pain may occur without an erection, caused by inflammation in the area of the developing plaques.

Mentzel *et al.* published a series of 30 EHE of soft tissues and they showed a median age of 50 years and female predominance. Five tumours were located in anogenital regions. With a median follow-up of 36 months, local recurrence was observed in three cases and systemic metastases in five cases. Finally, four patients (17%) died due to cancer. They conclude that more aggressive histologic features (striking nuclear atypia or more than two mitoses per 10 high-power fields) tended to be related to worse prognosis (22). The mitotic rate in our case was low, that is, ≤2 mitoses per 10 high-power fields. Therefore, it was classified as a low-grade EHE.

Because of its rarity, there is no standard treatment. According to Sardaro *et al.* (2), in a study of pulmonary EHE, when the lesions are small and limited in number,

some authors recommend surgical resection. Successful curative resection achieves good outcomes. The role of adjuvant chemotherapy and/or RT is ambiguous. Usually, RT after surgical resection is chosen for localized EHE, in order to control the residual disease given the recurrence of EHE, while chemotherapy is preferred in cases with widespread disease.

Limitations of this review are the scarcity of cases and short follow-up. These limitations prevent us from drawing strong conclusions.

This case report and the related literature review give some insights about the management of this rare tumour and may help clinicians recognize its clinical presentation. Nevertheless, it is crucial to improve future research and compile new reported cases to better establish the characteristics of EHE.

In conclusion, EHE is a malignant vascular tumour that rarely affects the penis. Local excision of the tumour, with re-excision or intraoperative margins assessment, is the best treatment. Systemic chemotherapy and RT can be used to treat locally advanced or widespread disease. Patients require a strict follow-up in order to detect early local recurrence.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/tau-21-277

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this study and any accompanying images.

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