

Rare Case of Atypical Epithelioid Hemangioma of Penis Initially Misdiagnosed as Peyronie's Disease: Report With Clinical, Radiologic, and Immunohistochemical Analysis

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We report a rare case of atypical epithelioid hemangioma of the penis in a 42-year-old man with a painful penile dorsal nodule, first misdiagnosed on simple penile ultrasonography as Peyronie's disease. Even though the patient underwent treatment, the lesion improved and a penile echo-color Doppler scan showed abundant vascularization. After local excision, the pathologic diagnosis was atypical epithelioid hemangioma (central epithelioid cells bordered by immature vessels), with immunohistochemical positivity for CD31 and CD34 and negativity for epithelial membrane antigen. At 12 months after surgery, the patient was free of disease. Penile echo-color Doppler ultrasonography is essential to perform a differential diagnosis between Peyronie's disease from other penile nodular diseases. UROLOGY 73: 210.e7–210.e10, 2009. © 2009 Elsevier Inc.

Epithelioid hemangioma (EH) is an uncommon benign vascular tumor.^{1,2} It is usually located in the subcutaneous tissues of the head and the distal portions of the extremities, especially the digits.¹ It generally presents as a tender nodule that slowly enlarges with time. The size at excision has ranged from 0.5 to 2.5 cm in greatest dimension. The mean time between the first appearance and its excision was 4.5 months, ranging from a few days to 1 year.¹

Microscopically, EH consists of a predominantly solid proliferation of endothelial cells with an epithelioid appearance.^{1–5} Nuclear atypia is modest or absent. The mitotic counts have ranged from 0 to 2 per 10 high-power fields, without atypical mitoses. At the center of the lesion, the cells are arranged in nests or small, sheet-like aggregates. At the periphery, they form immature, but well-defined, vessels, often with an abundant inflammatory infiltrate with lymphocytes and eosinophils.^{1,3–5}

EH comes in two forms: a "typical" (twice as frequent) and an "atypical" form. In the typical cases, well-formed, fully canalized vessels are found at the periphery with a defined smooth muscle coat. Atypical cases contain dominant areas with small, sheet-like aggregates of endothelial cells without definitive vessel formation.¹ Most importantly,

the atypical forms can prove to be the most problematic in the differential diagnosis of malignant vascular tumors.

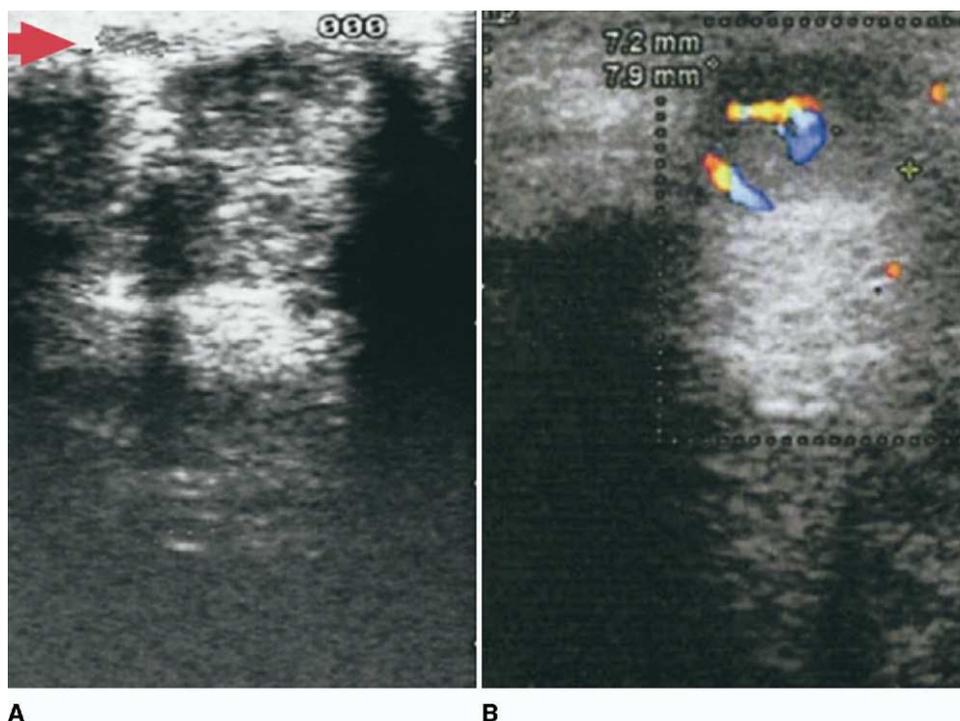
CASE REPORT

A 42-year-old man presented with a painful nodule located dorsally at the root of the left corpus cavernosum that had developed 4 years previously resulting from trauma during sexual intercourse. He had undergone penile ultrasonography, which had revealed a hypoechogenic ovoid formation ($4 \times 7 \times 5$ mm), dorsally located in the septum intercavernosum close to the tunica albuginea of the left corpus cavernosum (Fig. 1A). Initially, this lesion was interpreted as being Peyronie's disease (PD) and was treated with local iontophoresis (steroids and calcium antagonists). However, the patient reported continued penile pain and the sensation of lesion enlargement. He voluntarily interrupted treatment and, after 4 years, was eventually referred to our department. On physical examination, a solitary, painful, firm, well-circumscribed penile mass without superficial or deep inguinal lymph node enlargement was found. The patient reported no erectile dysfunction (International Index of Erectile Function-5 score of 25) and produced a photograph showing no deformity of the erect penis. Penile ultrasonography demonstrated a dorsal nodule with well-defined margins ($7 \times 10 \times 8$ mm) and echo-color Doppler (ECD) examination disclosed an abundantly vascularized lesion (Fig. 1B). Because of these dubious results, magnetic resonance imaging and computed tomography of the pelvis and abdomen were performed and proved

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Figure 1. (A) Bidimensional penile ultrasound scan, performed 4 years before surgical resection, showing hypoechoic lesion dorsally located in septum intercavernosum next to tunica albuginea of left corpus cavernosum (arrow). (B) Penile ECD ultrasound scan performed 1 month before surgery highlighting marked vascularization and volumetric lesion enlargement.

negative for neoplastic disease. The lesion (diameter 10 mm) was surgically excised. Microscopically, the lesion consisted of epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. The nuclear atypia was mild, and mitotic figures were absent. The nodule had a central zone (Fig. 2A) showing a solid growth pattern and a peripheral zone (Fig. 2B) containing immature, but well-formed, vessels. An abundant inflammatory infiltrate with lymphocytes and eosinophils was detected. A thin rim of connective tissue was present around the lesion. Immunohistochemical analysis (Fig. 3) revealed that the epithelioid cells were positive for CD31, CD34, and factor VIII. The stains for keratins and epithelial membrane antigen were negative. The pathologic diagnosis of EH, atypical variant, was rendered. Follow-up consisted of penile ECD ultrasonography and physical examination every 3 months. After 14 months, the patient was asymptomatic, with no evidence of local disease recurrence.

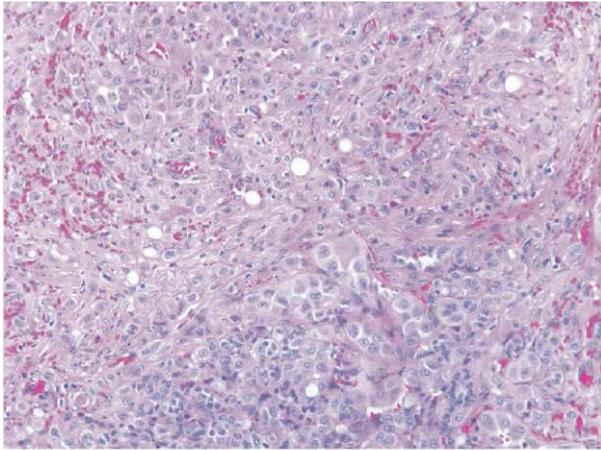
COMMENT

This case highlights the distinctive features of EH. First, most cases of EH develop in the head (in the distribution zone of the superficial temporal artery) and in the distal portion of the extremities.^{1,3} Only very rarely has this tumor been described to affect the penis, with fewer than 30 cases reported.^{1,3} In some patients, the association between EH and penile trauma has been identified.^{1,4} We

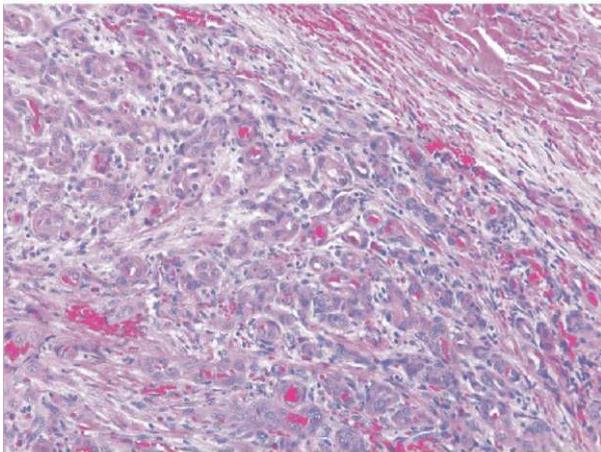
know from published studies that the reference standard for treatment of EH is local excision. External beam radiotherapy to the surgical margins is seldom performed. In only 1 case of atypical EH, did local recurrence develop 6 cm distal to the previous excision. At long-term follow-up (20 years at the most), nearly all patients remained free of disease. Neither lymph node involvement nor distant metastasis has been reported.^{1,3}

Second, the elapsed time between the initial diagnosis and the excision of the lesion in previously reported cases of EH was 1 year at the most.^{1,3} In contrast, in our patient, the interval was exceptional at 4 years. This could have been because of the greater depth of the lesion at the root of the corpus cavernosum and the increase in size that was slower than formerly described. Ultrasound time-elapsed measurements of the lesion demonstrated that, after 4 years, the greatest dimension had only increased by 3 mm. Therefore, in our case the “atypical” variant of EH was not associated with rapid growth of the lesion.

Third, this lesion was initially misdiagnosed as PD, and ECD ultrasonography was essential to the clinical diagnosis of EH. Ultrasonography showed a well-circumscribed hypoechoic PD-like nodule with a slightly irregular internal structure, in association with the tunica albuginea. PD nodules can have different ultrasound patterns, depending on their age and activity (normally hypoechoic in recent nodules, isoechoic in fibrotic nodules, and hyperechoic in calcific nodules).⁶ How-



A



B

Figure 2. Microscopic findings. **(A)** Central portion of lesion showing predominantly solid growth pattern of epithelioid endothelial cells. Occasional intracellular lumina are seen. Hematoxylin-eosin stain, original magnification $\times 100$. **(B)** Peripheral portion of lesion displaying well-formed vessels lined by epithelioid endothelial cells. Lesion was well circumscribed. Hematoxylin-eosin stain, original magnification $\times 100$.

ever, in some cases, even with the clinical presentation of PD, no significant alterations can be detected on ultrasonography.⁷ Nevertheless, vascularization assessment with penile ECD ultrasonography will help to establish the correct clinical diagnosis: PD nodules feature low or absent vascularization, usually surrounded by distorted vessels.^{8,9} In contrast, in the present case, ECD ultrasonography demonstrated a highly vascularized lesion with both arterial and venous flow. To our knowledge, no ECD examination of EH has previously been performed at other anatomic sites.^{10,11}

Finally, the pathologic findings were of primary importance for the final differential diagnosis between EH and other similar vascular lesions, including reactive vascular proliferations and benign and frankly malignant tumors.^{2,5}

Bacillary angiomatosis is a reactive vascular lesion that affects immunodepressed patients (especially the human immunodeficiency virus-positive population) and is due

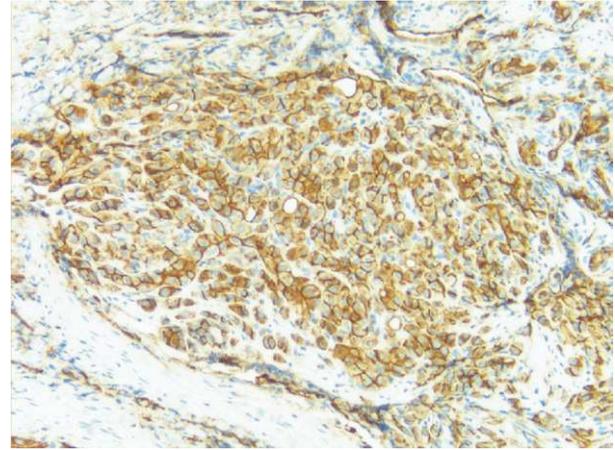


Figure 3. Immunohistochemical analysis. Strong and diffuse immunoreactivity for CD31 in neoplastic endothelial cells. Immunoperoxidase and hematoxylin counterstain, original magnification $\times 200$.

to local infection of the bacterium *Bartonella henselae*.¹² Microscopically, it differs from EH by its predominantly vasoformative architecture and the presence of neutrophils and bacteria aggregates, instead of eosinophils.

Epithelioid hemangioendothelioma is a borderline vascular tumor recurring locally and uncommonly causing distant metastases.¹³ Epithelioid endothelial cells are arranged in cords or sheet-like aggregates, with a mitotic count of fewer than five per 10 high-power fields. The features that distinguish it from EH include marked nuclear atypia, the presence of myxoid/hyalinized tissue matrix, and the absence of eosinophils in the inflammatory infiltrate.

Epithelioid angiosarcoma is a high-grade vascular neoplasm associated with a high rate of lymph node and distant metastasis, as well as high mortality. It features epithelioid endothelial cells growing in a solid pattern; however, it is characterized by aggressive histologic features (eg, destructive growth, necrosis, and a high mitotic rate with atypical mitoses).¹⁴

CONCLUSIONS

The results of our study have shown that to perform a correct clinical differential diagnosis of PD from other rare entities presenting with growing penile nodules, such as EH, a penile ECD evaluation is essential, especially in younger men. In case of doubt as to the diagnosis, surgical excision of the lesion should be performed, first to determine the definitive diagnosis by immunohistochemical analysis (PD or rare penile vascular neoplasms) and second to establish the final therapy, whether conservative or radical penile surgery.

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