

## QUIZ CASES

# A rare case of cellular epithelioid hemangioma involving the penis

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**KEYWORDS:** epithelioid angiomatous nodule, epithelioid angiosarcoma, epithelioid hemangioendothelioma, epithelioid hemangioma, FOSB, vascular neoplasm

## 1 | CASE

A 67-year-old white male presented with a subcutaneous mass at the base of the penis (Figures 1–3). What is your diagnosis?

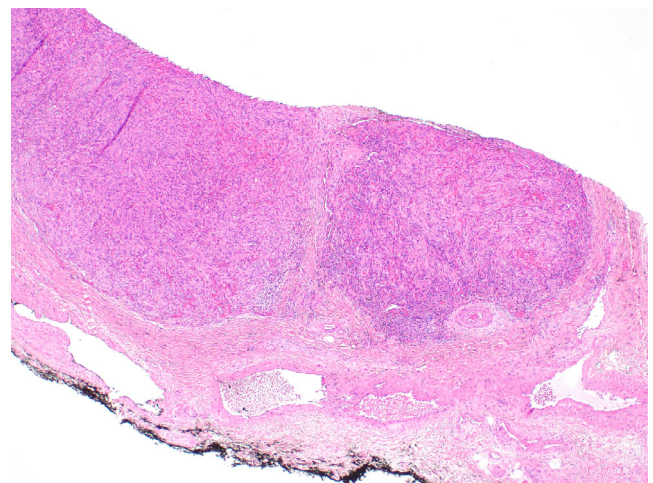
## 2 | INTRODUCTION

Epithelioid hemangioma (EH) is a benign vascular tumor of the skin and subcutaneous tissue that presents clinically as a small red to violaceous papule or plaque with an average size of 1 cm.<sup>1,2</sup> EH most commonly affects young adults aged 20–50 years, classically in the head, neck, and distal extremity regions, although a wide range of additional anatomic locations may be involved including the trunk, deep soft tissue, bone, lung, lymph nodes, colon, eye, and spleen.<sup>1,2</sup> Only rarely has EH been reported to affect the penis, where histopathologic evaluation often reveals a highly cellular neoplasm that can cause concern for a malignant vascular tumor such as epithelioid hemangioendothelioma (EHE) or epithelioid angiosarcoma.<sup>1,3,4</sup> Immunohistochemistry may aid in definitive diagnosis when such histopathologic overlap occurs.<sup>5–11</sup>

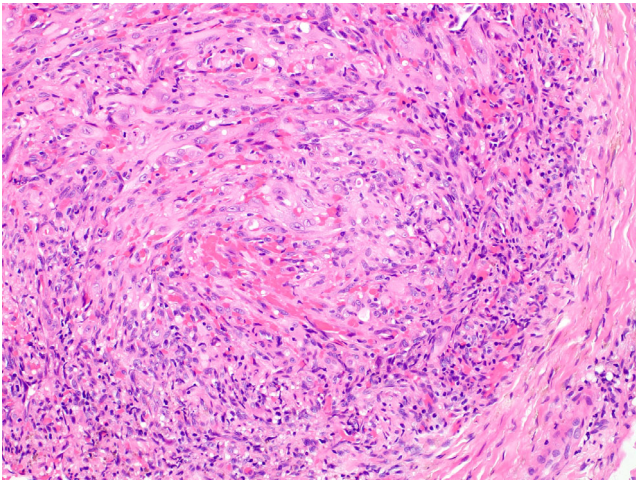
## 3 | CASE REPORT

A 67-year-old white man presented with a subcutaneous mass at the base of the penis. Histopathologic evaluation revealed a circumscribed subcutaneous mass that was vaguely nodular at low power (Figure 1). A prominent inflammatory cuff was present that was composed

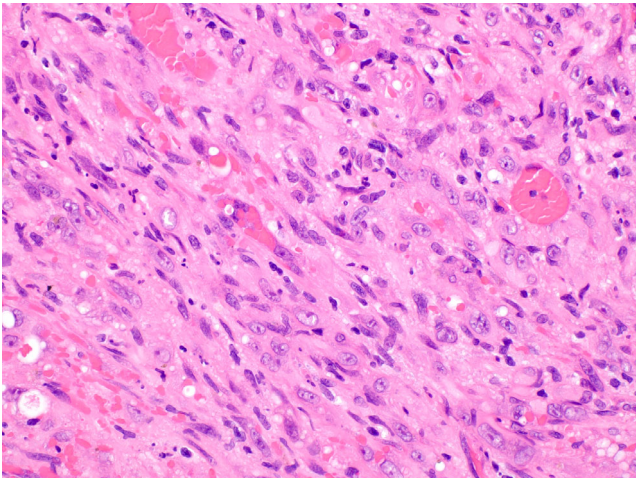
primarily of lymphocytes with rare eosinophils (Figure 2). Evidence of vasoformation was present. High magnification revealed epithelioid cells with vesicular chromatin and central distinct nucleoli without high-grade cytologic atypia or mitotic activity (Figure 3). The histopathologic appearances raised consideration for several entities including EHE, epithelioid angiosarcoma, epithelioid angiomatous nodule, and EH. Immunohistochemistry showed strong expression of ERG (Figure 4A), supporting vascular differentiation, as well as FOSB (Figure 4B), suggestive of an underlying *FOSB* rearrangement. Tumor cells were negative for CAMTA1 and human herpesvirus-8.



**FIGURE 1** Histopathologic evaluation revealed an apparently well-circumscribed and cellular subcutaneous mass that was vaguely nodular at low power (H&E). Original magnification:  $\times 40$



**FIGURE 2** Higher magnification revealed cellular nodules containing epithelioid cells with a surrounding inflammatory infiltrate composed primarily of lymphocytes (H&E). Rare eosinophils were present. Occasional vasoformative areas were identified. Original magnification:  $\times 200$



**FIGURE 3** High magnification revealed plump spindled to epithelioid cells with vesicular chromatin, distinct, centrally located nucleoli, and abundant pale eosinophilic cytoplasm (H&E). Mitotic activity was not conspicuous. Original magnification:  $\times 400$

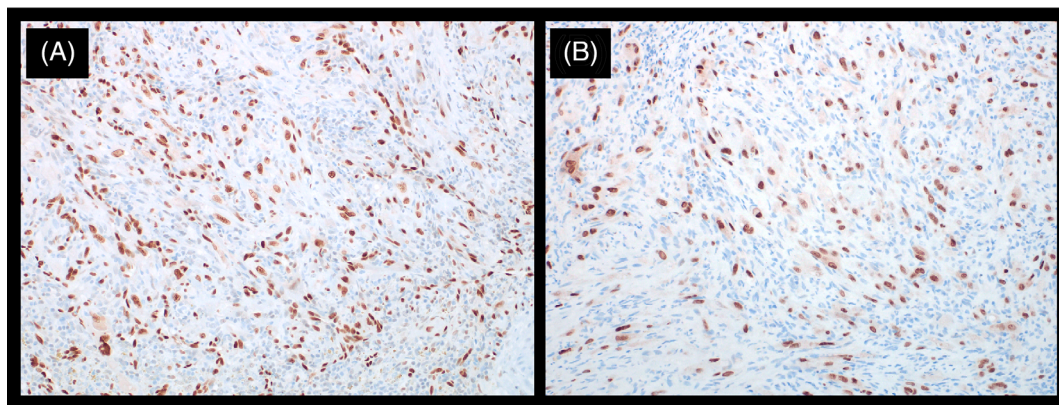
Given this immunohistochemical profile, in addition to the lack of mitotic activity or high-grade cytologic atypia, a diagnosis of the cellular EH was made.

#### 4 | DISCUSSION

EH is a dermal or subcutaneous tumor that appears as a circumscribed and vaguely nodular mass with vascular spaces lined by histiocytoid to epithelioid endothelial cells often having vesicular chromatin and variably prominent nucleoli.<sup>1,2</sup> At its periphery, EH classically displays a variably pronounced background inflammatory infiltrate, predominantly consisting of lymphocytes.<sup>1,2</sup> Numerous eosinophils are not required but may be present.<sup>10</sup> A subset of cases occurs intravascularly.

The morphologic spectrum of EH exhibits a wide range of appearances. EH can be subdivided into three major histopathologic variants: conventional, cellular, and angiolymphoid hyperplasia with eosinophilia (ALHE).<sup>12</sup> Conventional or typical EH is well-circumscribed at low magnification, may be associated with a single small, thick-walled artery, and often is surrounded by a prominent peripheral lymphoid reaction.<sup>3</sup> The histiocytoid to epithelioid endothelial cells contain an enlarged nucleus with vesicular chromatin; however, multilayering is typically not seen. The ALHE variant shares similarities with conventional EH, but subcutaneous examples may have a discontinuous and multinodular appearance with less well-defined margins. As its name suggests, it is associated with an eosinophil-rich lymphocytic infiltrate which may contain numerous reactive germinal centers and may be localized to deep soft tissue or bone.<sup>13</sup> Cellular EH, which has a predilection for the penis and is also referred to as the “atypical” or “exuberant” type in the literature, differs from conventional EH given the presence of cellular nodules of tumor cells.<sup>3</sup> In addition to this finding, cellular EH may show low-level mitotic activity, mild-to-moderate nuclear pleomorphism, and focal necrosis.<sup>3,14</sup> While nuclei may be enlarged with irregular contouring, high-grade cytologic atypia is notably absent.

Multiple recurrent gene rearrangements have been identified in the pathogenesis of EH. The current literature identifies recurrent *FOS* and *FOSB* gene alterations in one-third of EHs, although incidence differs according to anatomic location.<sup>5,10,14,15</sup> Recent studies



**FIGURE 4** Immunohistochemistry showing diffuse expression of ERG (A) and FOSB (B). Original magnifications:  $\times 200$



have shown that a subset of EHs with atypical features harbor rearrangements involving the *FOSB* gene, a finding also seen in cases of EH occurring in bone and in pseudomyogenic hemangioendothelioma (epithelioid-sarcoma-like hemangioendothelioma).<sup>5,8-10,12,14</sup> More recently, the novel *GATA6-FOXO1* fusion was described in a subset of EHs occurring in the skin or subcutaneous tissue. Antonescu et al<sup>15</sup> suggest that gene fusions in EH may not correlate with histopathologic features but with anatomic location, with *FOS*-related fusions occurring more commonly in EH of the bone,<sup>5</sup> *FOSB* rearrangements in tumors of the penis,<sup>14</sup> and *GATA6-FOXO1* in the skin and head and neck.<sup>15</sup> These genetic abnormalities have not been detected in the ALHE variant and may point to a pathogenesis distinct from EH with gene rearrangements.<sup>5,10</sup>

In comparison, EHE was originally described as a vascular tumor of intermediate malignancy, but is now thought of as a true sarcoma by many authors because of its risk of recurrence and distant metastasis.<sup>7</sup> This tumor most commonly presents in deep soft tissue, bone, lung, liver, and skin and is composed of large epithelioid endothelial cells with abundant glassy eosinophilic cytoplasm arranged in single units, nests, or cords.<sup>13</sup> Intracytoplasmic vacuoles are commonly seen.<sup>13</sup> A locally aggressive tumor, margins may show infiltration, although mitotic activity, atypia, and necrosis are usually minimal in most cases, if present. A subset of EHEs denoted “malignant” or “high-risk” tumors have worrisome histopathologic features including sheet-like growth, increased mitotic activity, necrosis, and/or pleomorphism.<sup>10,13</sup> While multiple risk stratification systems have been proposed, current studies suggest that combination of tumor size and measures of histopathologic atypia<sup>16</sup> or mitotic rate<sup>17</sup> may be most predictive of adverse outcome. Interestingly, synaptophysin expression may be observed in a subset of high-risk cases.<sup>16</sup> Most EHEs harbor *WWTR1-CAMTA1* rearrangements, which can be detected by molecular means and by *CAMTA1* immunohistochemistry.<sup>6,7,13</sup> Exceptions to *CAMTA1* expression include a minority of cases that instead show *TFE3* overexpression due to *YAP1-TFE3* rearrangements and a rare subset of cardiac EHE with variant *WWTR1* fusion partners.<sup>11,16</sup>

Epithelioid angiosarcoma is a highly aggressive endothelial cell malignancy, most commonly arising in the deep soft tissues of the extremities.<sup>13</sup> Epithelioid angiosarcoma shows malignant histopathologic features such as infiltrative or sheet-like growth, abundant mitotic activity, prominent nuclear pleomorphism, hyperchromasia, and necrosis.<sup>13</sup> Epithelioid angiosarcoma often displays rudimentary vasoformative architecture with large, irregular vascular channels lacking canalization or cystically dilated spaces. A pseudopapillary architectural pattern is sometimes seen.

Epithelioid angiomatous nodule is typically a well circumscribed, unilobular, dermal-based lesion without obvious vascular channels composed of epithelioid endothelial cells with eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli.<sup>18</sup> Epithelioid angiomatous nodule does not typically extend into the subcutis.<sup>18</sup> An abundant infiltrate of lymphocytes and eosinophils may be present.<sup>18</sup> Of note, *FOSB* is not expressed in epithelioid angiomatous nodule.<sup>12</sup>

Pseudomyogenic hemangioendothelioma, also known as epithelioid-sarcoma-like hemangioendothelioma, is an indolent vascular neoplasm with a predilection for the extremities of young adult males and has a characteristic multifocal presentation.<sup>12</sup> Histopathologically, pseudomyogenic hemangioendothelioma contains sheets of plump spindled to epithelioid cells with abundant eosinophilic cytoplasm.<sup>12</sup> Unlike EH, this tumor lacks vasoformation and is commonly associated with a neutrophilic infiltrate.<sup>12</sup> Recurrent rearrangements of *SERPINE1-FOSB* and *ACTB-FOSB* are found in pseudomyogenic hemangioendothelioma.<sup>12,19</sup> In addition, case reports of novel *FOSB* fusion partners with *WWTR1*, *CLTC*, *EGFL7*, and *POTE1* have been recently reported.<sup>9,20-22</sup> This leads to overexpression of *FOSB*, causing possible confusion with EH.<sup>12</sup>

T-cell-rich angiomatoid polypoid pseudolymphoma (TRAPP) of the skin is a recently described variant of cutaneous pseudolymphoma.<sup>23</sup> Clinically, it presents as a solitary polypoid lesion in non-acral sites in adults, primarily on the head and neck and trunk. Lesions are characterized histopathologically by a T-cell-rich lymphoplasmahistiocytic dermal infiltrate and prominent vascular channels lined by plump endothelial cells.<sup>23</sup> More recently, a case series by Santa Cruz et al<sup>24</sup> suggested solitary vascular proliferations with a dense lymphoid tissue reaction, including TRAPP of the skin and other similar entities, may exist on a spectrum. The authors proposed the term inflammatory lobular hemangioma (ILH) to encompass these lobular vascular proliferations with dense lymphocytic infiltrates.<sup>24</sup> While similar, ILH differs from EH histopathologically because of a higher degree of inflammation, lobular configuration, and less frequent presence of characteristic epithelioid endothelial cells.

## 5 | CONCLUSIONS

EH may pose a significant diagnostic challenge because of its morphologic variability. EH of the penis, although rare, is often of the cellular subtype and thus must be distinguished from malignant vascular tumors with metastatic potential. A lobular growth pattern, vascular channel formation, and minimal cellular atypia or mitotic activity support EH over its malignant counterparts including EHE or epithelioid angiosarcoma. Immunohistochemistry can aid in definitive diagnosis. Because most cases of EHE harbor rearrangements of the *CAMTA1* gene, IHC for *CAMTA1* is particularly useful when differentiating EHE from EH, as shown in this case.<sup>5,8-10,12</sup> When combined with clinical and histopathologic findings, the presence of *FOSB* expression may support a diagnosis of cellular EH.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## REFERENCES

1. Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia. A clinicopathologic study of 116 patients. *J Am Acad Dermatol*. 1985; 12(5 Pt 1):781-796.
2. Guo R, Gavino ACP. Angiolymphoid hyperplasia with eosinophilia. *Arch Pathol Lab Med*. 2015;139(5):683-686.
3. Fetsch JF, Sesterhenn IA, Miettinen M, Davis CJ. Epithelioid hemangioma of the penis: a clinicopathologic and immunohistochemical analysis of 19 cases, with special reference to exuberant examples often confused with epithelioid hemangioendothelioma and epithelioid angiosarcoma. *Am J Surg Pathol*. 2004;28(4):523-533.
4. Mutgi KAJ, Swick BL. Multifocal epithelioid hemangioma of the penis: a diagnostic and therapeutic challenge. *J Cutan Pathol*. 2015;42(5):303-307.
5. Huang SC, Zhang L, Sung YS, et al. Frequent FOS gene rearrangements in epithelioid hemangioma: a molecular study of 58 cases with morphologic reappraisal. *Am J Surg Pathol*. 2015;39(10):1313-1321.
6. Jung H, Kim HN, Jang Y, Park CK, Ha SY. CAMTA-1 expression in 24 cases of hepatic epithelioid hemangioendothelioma in a single institute: diagnostic utility for differential diagnosis from hepatic angiosarcoma. *In Vivo*. 2019;33(6):2293-2297.
7. Doyle LA, Fletcher CDM, Hornick JL. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. *Am J Surg Pathol*. 2016;40(1):94-102.
8. Tsuda Y, Suurmeijer AJH, Sung YS, Zhang L, Healey JH, Antonescu CR. Epithelioid hemangioma of bone harboring FOS and FOSB gene rearrangements: a clinicopathologic and molecular study. *Genes Chromosomes Cancer*. 2021;60(1):17-25.
9. Panagopoulos I, Lobmaier I, Gorunova L, Heim S. Fusion of the genes WWTR1 and FOSB in pseudomyogenic hemangioendothelioma. *Cancer Genomics Proteomics*. 2019;16(4):293-298.
10. Torrence D, Antonescu CR. The genetics of vascular tumours: an update. *Histopathology*. 2022;80(1):19-32.
11. Suurmeijer AJH, Dickson BC, Swanson D, Sung YS, Zhang L, Antonescu CR. Variant WWTR1 gene fusions in epithelioid hemangioendothelioma: a genetic subset associated with cardiac involvement. *Genes Chromosomes Cancer*. 2020;59(7):389-395.
12. Hung YP, Fletcher CDM, Hornick JL. FOSB is a useful diagnostic marker for pseudomyogenic hemangioendothelioma. *Am J Surg Pathol*. 2017;41(5):596-606.
13. Antonescu C. Malignant vascular tumors—an update. *Mod Pathol*. 2014;27(Suppl 1):S30-S38.
14. Antonescu CR, Chen HW, Zhang L, et al. ZFP36-FOSB fusion defines a subset of epithelioid hemangioma with atypical features. *Genes Chromosomes Cancer*. 2014;53(11):951-959.
15. Antonescu CR, Huang SC, Sung YS, et al. Novel GATA6-FOXO1 fusions in a subset of epithelioid hemangioma. *Mod Pathol*. 2021; 34(5):934-941.
16. Shibayama T, Makise N, Motoi T, et al. Clinicopathologic characterization of epithelioid hemangioendothelioma in a series of 62 cases: a proposal of risk stratification and identification of a synaptophysin-positive aggressive subset. *Am J Surg Pathol*. 2021;45(5):616-626.
17. Deyrup AT, Tighiouart M, Montag AG, Weiss SW. Epithelioid hemangioendothelioma of soft tissue: a proposal for risk stratification based on 49 cases. *Am J Surg Pathol*. 2008;32(6):924-927.
18. Gupta D, Kumari R, Jacob SE, Rajesh NG, Thappa DM. Cutaneous epithelioid angiomatous nodule versus epithelioid hemangioma: a dilemma. *Indian J Dermatol Venereol Leprol*. 2017;83(1):99-101.
19. Agaram NP, Zhang L, Cotzia P, Antonescu CR. Expanding the spectrum of genetic alterations in pseudomyogenic hemangioendothelioma with recurrent novel ACTB-FOSB gene fusions. *Am J Surg Pathol*. 2018; 42(12):1653-1661.
20. Bridge JA, Sumegi J, Royce T, Baker M, Linos K. A novel CLTC-FOSB gene fusion in pseudomyogenic hemangioendothelioma of bone. *Genes Chromosomes Cancer*. 2021;60(1):38-42.
21. Hakar MH, White K, Hansford BG, Swensen J, Davis JL. Novel EGFL7-FOSB fusion in pseudomyogenic haemangioendothelioma with widely metastatic disease. *Histopathology*. 2021;79(5): 888-891.
22. Gersmann AK, Haller F, Behnert N, et al. Primary pseudomyogenic haemangioendothelioma of the testis with a novel POTE1::FOSB gene fusion. *Histopathology*. 2022. [Epub ahead of print].
23. Dayrit JF, Wang WL, Goh SGN, Ramdial PK, Lazar AJF, Calonje E. T-cell-rich angiomatoid polypoid pseudolymphoma of the skin: a clinicopathologic study of 17 cases and a proposed nomenclature. *J Cutan Pathol*. 2011;38(6):475-482.
24. Santa Cruz D, Plaza JA, Wick MR, Gru AA. Inflammatory lobular hemangioma: a vascular proliferation with a prominent lymphoid component. Review of a series of 19 cases. *J Cutan Pathol*. 2021; 48(2):229-236.

**How to cite this article:** Frecentese GI, Pantanowitz L, Patel RM, Bresler SC. A rare case of cellular epithelioid hemangioma involving the penis. *J Cutan Pathol*. 2022;1-4. doi:[10.1111/cup.14285](https://doi.org/10.1111/cup.14285)