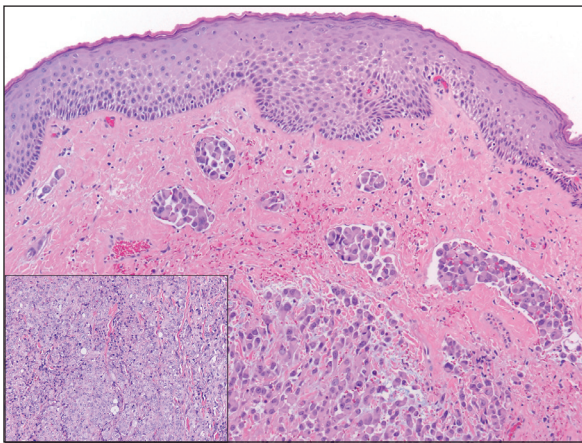


Painless Vulvar Nodule

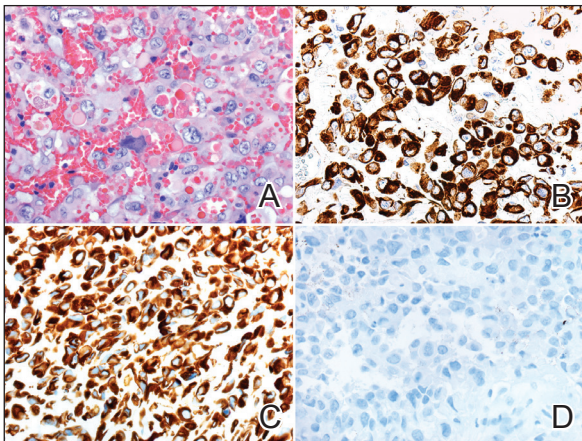
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H&E, original magnification $\times 10$ (inset: H&E, original magnification $\times 4$).



A: H&E, original magnification $\times 60$; B: CAM5.2, original magnification $\times 40$; C: vimentin, original magnification $\times 40$; D: INI-1, original magnification $\times 40$.

A 45-year-old woman with no notable medical history presented with a small nodule in the left pubic region lateral to the left labia majora. The lesion grew to 8 cm over the course of several months, and she underwent a simple excision for what clinically appeared to be a cyst.

THE BEST DIAGNOSIS IS:

- epithelioid angiosarcoma
- melanoma
- myoepithelial carcinoma
- poorly differentiated squamous cell carcinoma
- proximal-type epithelioid sarcoma

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The authors report no conflict of interest.

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THE DIAGNOSIS: Proximal-Type Epithelioid Sarcoma

Proximal-type epithelioid sarcoma (PES) is a rare high-grade sarcoma of uncertain histogenesis that may present with a benign clinical appearance. Proximal-type epithelioid sarcoma peaks at 20 to 40 years of age and has a slight male predominance. This tumor exhibits aggressive behavior with both local recurrence and metastasis.¹ The average overall survival is poor; however, tumor size less than 5 cm and complete excision with tumor-free margin status improves the prognosis.² Proximal-type epithelioid sarcoma should not be confused with distal-type epithelioid sarcoma, which has a better prognosis and occurs in younger patients.¹ Treatment of PES is wide excision, and chemotherapy trials with tazemetostat are ongoing.³

The deceptively banal clinical appearance of PES may delay appropriate diagnosis and treatment. Proximal-type epithelioid sarcoma often grows in sheets (quiz image [top] inset) and loose nests¹ but also may take on a more corded appearance mimicking myoepithelial carcinoma. The cells themselves are plump dyscohesive epithelioid cells (quiz image [top]) with large nucleoli and eosinophilic cytoplasm or hyaline globules¹ (quiz image [bottom]), but cells also may be focally spindle. Myxoid stroma, hemorrhage, and necrosis often are prominent features. Epithelioid sarcomas characteristically demonstrate positive immunostaining for both epithelial and mesenchymal markers (pan-cytokeratin and vimentin),¹ with the majority having loss of expression of integrase interactor 1 (INI-1).² Histology in this case was positive for cytokeratin monoclonal antibodies CAM5.2 and OSCAR, epithelial membrane antigen, and vimentin; it showed loss of INI-1 staining (quiz image [bottom]). Negative stains included S-100, p63, cytokeratins 7 and 20, CD34, CD31, ERG, glial fibrillary acidic protein, transducin-like enhancer of split 1, CD117, myogenin, synaptophysin, chromogranin, CD10, inhibin, CD99, and estrogen receptor.

The differential diagnosis of PES includes poorly differentiated squamous cell carcinoma (Figure 1 [inset]), melanoma, myoepithelial carcinoma, and epithelioid angiosarcoma. Primary squamous cell carcinoma of the vulva presents as an endophytic or exophytic mass with raised borders. Vulvar cancer is uncommon among gynecologic malignancies, with squamous cell carcinoma being the most commonly encountered.⁴ Vulvar intraepithelial neoplasia (VIN) is increasing in incidence, while the occurrence of invasive squamous cell carcinoma remains stable.⁵ Human papillomavirus-related VIN (usual-type VIN) is less likely to progress to squamous cell carcinoma than differentiated VIN (d-VIN), a dysplasia that is unrelated to human papillomavirus that frequently harbors p53 mutations.⁴ The presence of histologic epidermal involvement can help distinguish squamous cell carcinoma from PES (Figure 1).

As opposed to PES, metastatic squamous cell carcinoma is characterized by intercellular bridges and often at least focal keratinization (Figure 1). Squamous cell carcinoma demonstrates positivity with p63 and p40 immunohistochemical stains, while PES rarely stains for either.⁶

Melanoma is the second most common vulvar malignancy. Vulvar melanoma tends to occur in women of advanced age but has been reported in girls as young as 10 years old.⁷ There is some evidence that patients with lichen sclerosus may be at an increased risk for the development of vulvar melanoma.⁸ Compared to PES, primary vulvar melanoma usually demonstrates epidermal involvement as well as clinical findings of a pigmented lesion (Figure 2). A notable minority of vulvar melanomas are amelanotic.⁹ Melanoma may be distinguished from PES with a panel of melanocytic markers—human melanoma black 45, Melan-A, SRY-box transcription factor 10, S-100, and microphthalmia transcription factor—that rarely are expressed in the latter. Both PES and rhabdoid melanoma have eosinophilic and tinctorial cytoplasmic inclusions.¹⁰ Melanin pigment and more cohesive nests are helpful clues that may point to melanoma when present.

Myoepithelial carcinoma of the vulva is rare.¹¹ Myoepithelial carcinoma of soft tissue is more aggressive than its benign counterpart, with up to a 50% metastasis rate.¹² The presence of prominent corded or trabecular growth in a myxoid or hyaline background may point to the diagnosis (Figure 3). Similar to PES, myoepithelial carcinoma may lose expression of nuclear INI-1, while myoepithelial carcinoma is more likely to express S-100 and glial fibrillary acidic protein.¹³ Rearrangements of EWS RNA

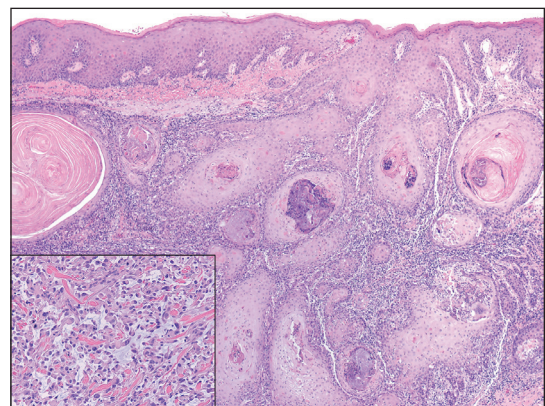


FIGURE 1. A well-differentiated squamous cell carcinoma with prominent keratinization with endophytic and expansile growth (H&E, original magnification $\times 4$). A poorly differentiated squamous cell carcinoma with prominent myxoid background and dyscohesive cells (H&E, original magnification $\times 20$ [inset]).

binding protein 1, *EWSR1*, have been found in half of myoepithelial neoplasms.¹²

Angiosarcomas represent 5% of cutaneous sarcomas and rarely have been reported in the vulva, primarily occurring in the setting of long-standing lymphedema and radiation.¹⁴ Angiosarcoma more often occurs on the head and neck, breasts, or extremities. Additional risk factors for the development of angiosarcoma include toxin exposure (eg, polyvinyl chloride, thorium dioxide, arsenic), anabolic steroids, and filariasis, as well as genetic disorders (eg, neurofibromatosis type 1, *BRCA* gene mutations, Maffucci syndrome).¹⁵ Epithelioid angiosarcoma is an infiltrative tumor composed of irregular anastomosing vascular channels with extravasated erythrocytes (Figure 4). Solid growth and necrosis may be present in more aggressive tumors. The cells themselves are pleomorphic endothelial cells with vesicular chromatin and prominent nucleoli. Epithelioid angiosarcoma may resemble carcinoma and have focal keratin expression. However, the characteristic eosinophilic cytoplasm seen in PES should not be identified in epithelioid angiosarcoma.

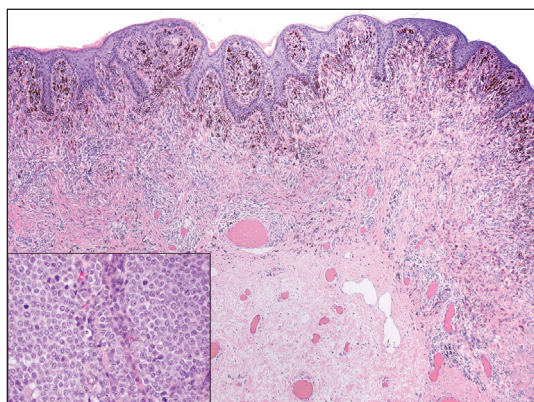


FIGURE 2. Melanoma. Junctional component, nests, and prominent melanin (H&E, original magnification $\times 4$). Prominent nucleoli and amphophilic cytoplasm (H&E, original magnification $\times 40$ [inset]).

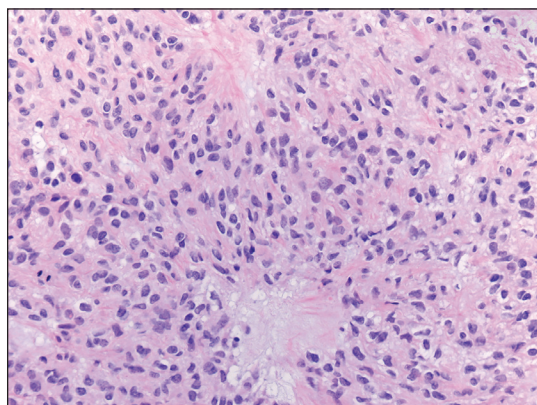


FIGURE 3. Myoepithelial carcinoma. Basophilic angulated nuclei with clear cytoplasm in a loose fibrous to myxoid stroma (H&E, original magnification $\times 20$).

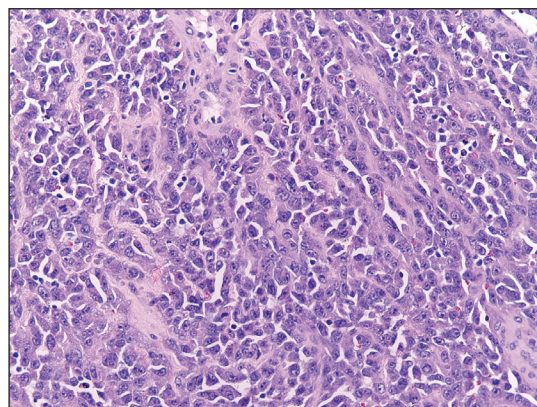


FIGURE 4. Angiosarcoma. Cords of epithelioid cells forming slitlike vascular channels (H&E, original magnification $\times 20$).

Unlike PES, epithelioid angiosarcoma is positive for CD31 and has retained expression for INI-1. Both angiosarcoma and proximal-type epithelioid sarcoma may express vascular markers CD34 and FLI-1¹⁶; thus an expanded panel of immunohistochemical studies may be of utility.

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