Painful, erythematous, and ulcerated nodules on the thigh

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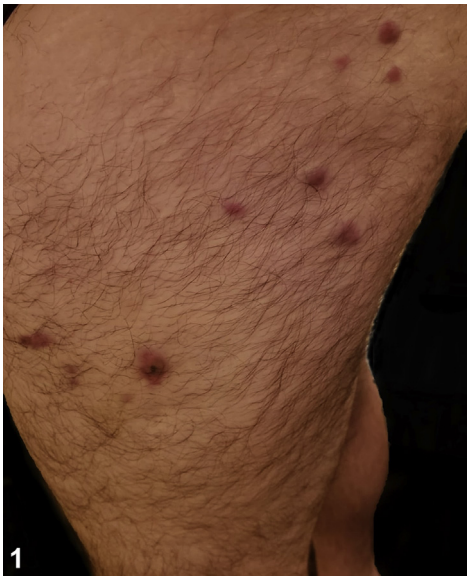

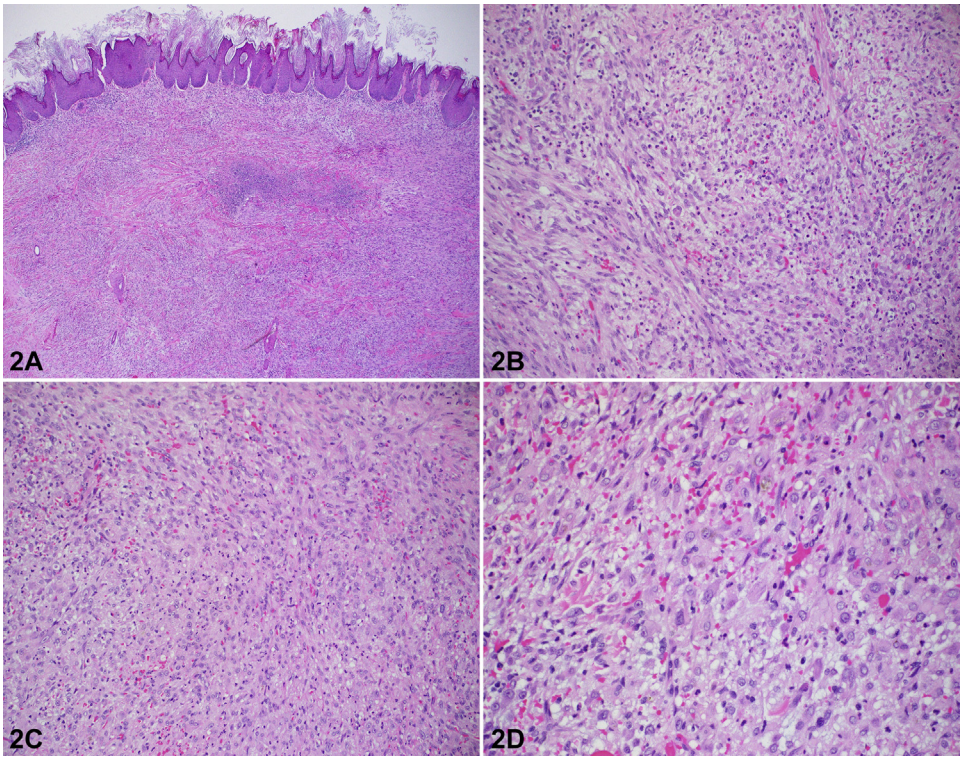

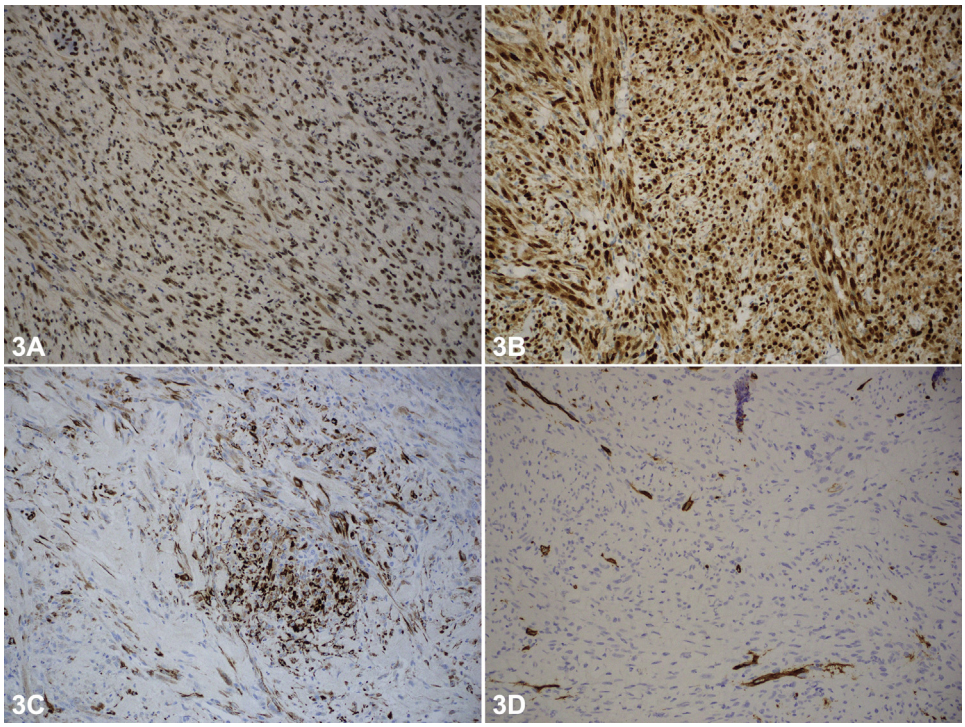

A 27-year-old man with no significant past medical history presented due to concern for bumps on his leg that had persisted for several months. On physical examination, multiple firm pink nodules ranging from 1 to 3 cm were observed on the lateral aspect of the left thigh, some of which were ulcerated (Fig 1). An excisional biopsy was performed, which revealed spindled-to-epithelioid cells with infiltrative borders and focal neutrophilic infiltrate (Fig 2). The lesional cells stained for pancytokeratin (AE1/AE3), CD31, *ETS*-related gene (ERG), and integrase interactor 1 (INI1), and were negative for CD34, S100, and factor XIIIa (Fig 3).

Question 1: What is the diagnosis?

A. Acute folliculitis

B. Cellular dermatofibroma

C. Dermatofibrosarcoma protuberans

D. Epithelioid sarcoma

E. Pseudomyogenic hemangioendothelioma

Answers:

A. Acute folliculitis — Incorrect. The clinical picture accompanied by the presence of a neutrophilic infiltrate could lead one to consider this diagnosis; however, the histologic picture of a spindled-to-epithelioid lesion with infiltrative borders points to a neoplastic process. A neutrophilic infiltrate is observed in approximately half of pseudomyogenic hemangioendotheliomas.[1]

B. Cellular dermatofibroma — Incorrect. Dermatofibroma is comprised of a variably cellular proliferation of spindled cells with entrapment of peripheral collagen fibers and induction of the overlying epidermis, rather than the verruciform hyperplasia observed here. Additionally, dermatofibromas express factor XIIIa and will not stain with pancytokeratin or ERG.

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C. Dermatofibrosarcoma protuberans — Incorrect. While dermatofibrosarcoma protuberans does have infiltrative borders, the negativity for CD34 in addition to the pancytokeratin and ERG positivity argues against this diagnosis.

D. Epithelioid sarcoma — Incorrect. Pseudomyogenic hemangioendothelioma can clinically and histologically mimic epithelioid sarcoma and was once thought to be a variant of epithelioid sarcoma.[2] Further characterization has found that pseudomyogenic hemangioendotheliomas have a unique immunohistochemical staining profile and translocations involving FosB proto-oncogene, AP-1 transcription factor subunit (FOSB) on chromosome 19.[3] Additionally, pseudomyogenic hemangioendothelioma retains expression of INI1.

E. Pseudomyogenic hemangioendothelioma — Correct. Also known as epithelioid sarcoma-like hemangioendothelioma, the clinical picture of a young man with multiple lower-extremity lesions accompanied by the histologic findings and immunohistochemical profile is the typical presentation of pseudomyogenic hemangioendothelioma.[1]

Question 2: Microscopically, pseudomyogenic hemangioendothelioma can mimic epithelioid sarcoma in that there can be areas of geographic necrosis and atypia. Which of the following immunohistochemical staining profiles is most consistent with pseudomyogenic hemangioendothelioma?

A. INI1 loss, pancytokeratin^{-}, ERG^{-}

B. INI1 loss, pancytokeratin^{+}, ERG^{-}

C. INI1 retention, pancytokeratin^{-}, ERG^{-}

D. INI1 retention, pancytokeratin^{-}, ERG^{+}

E. INI1 retention, pancytokeratin^{+}, ERG^{+}

Answers:

A. INI1 loss, pancytokeratin^{-}, ERG^{-} — Incorrect. INI1 loss would be concerning for an INI1-deficient malignancy, such as epithelioid sarcoma, but not pseudomyogenic hemangioendothelioma. Both tumors reliably express pancytokeratin, while ERG expression would be expected in pseudomyogenic hemangioendothelioma.

B. INI1 loss, pancytokeratin^{+}, ERG^{-} — Incorrect. INI1 loss and pancytokeratin expression in this clinical context would be more consistent with epithelioid sarcoma. Additionally, ERG positivity is expected in pseudomyogenic hemangioendothelioma.

C. INI1 retention, pancytokeratin^{-}, ERG^{-} — Incorrect. Presence of pancytokeratin staining is one of the defining features of both epithelioid sarcoma and pseudomyogenic hemangioendothelioma. The former would be expected to show loss of INI1, while the latter would express ERG.

D. INI1 retention, pancytokeratin^{-}, ERG^{+} — Incorrect. ERG is a marker of vascular origin, and positivity in conjunction with pancytokeratin negativity would point to another lesion, likely of vascular origin.

E. INI1 retention, pancytokeratin^{+}, ERG^{+} — Correct. While both epithelioid sarcoma and pseudomyogenic hemangioendothelioma may express ERG, nearly all epithelioid sarcomas show loss of INI1, whereas pseudomyogenic hemangioendotheliomas show retention.[3]

Question 3: Following the initial diagnosis of pseudomyogenic hemangioendothelioma, which of the following would be the next best step in management?

A. Amputation of the left lower extremity

B. Chemotherapy

C. Fluorodeoxyglucose-positron emission tomography and whole-body magnetic resonance imaging

D. Three months of observation

E. Wide local excision of all clinically apparent lesions

Answers:

A. Amputation of the left lower extremity — Incorrect. Prior to surgery, the patient should be evaluated for multifocality of disease. Amputation may be indicated in some cases, depending on the extent of disease.

B. Chemotherapy — Incorrect. Chemotherapy may be beneficial; however, experience is limited. The mechanistic target of rapamycin (mTOR) inhibitors have shown promise in management of nonresectable disease and have a less toxic profile than taxanes, anthracyclines, and platins.[4]

C. Fluorodeoxyglucose-positron emission tomography and whole-body magnetic resonance imaging — Correct. Pseudomyogenic hemangioendotheliomas are typically hypermetabolic. Positron emission tomography followed by whole-body magnetic resonance imaging is able to identify deep-seated lesions that may not be clinically

apparent.[5] Metastasis is rare but has been reported.[1]

D. Three months of observation − Incorrect. These lesions are locally aggressive and often multifocal. Follow-up with imaging is warranted to evaluate the full extent of disease.

E. Wide local excision of all clinically apparent lesions − Incorrect. This may be appropriate if the lesion has been confirmed unifocal by imaging. In this case, suspicion was high for multifocality due to the clinical presence of multiple nodules on the lateral aspect of the left thigh.

Abbreviations used:

ERG: *ETS*-related gene
INI1: integrase interactor 1

Conflicts of interest

None disclosed.

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