

Enlarging Nodule on the Thigh

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H&E, original magnification $\times 40$.

A 68-year-old patient presented with an enlarging flesh-colored nodule on the thigh that was positive for cytokeratin 20 and negative for cytokeratin 7.

THE BEST DIAGNOSIS IS:

- cutaneous endometriosis
- metastatic adenocarcinoma of the colon
- metastatic breast carcinoma
- primary cutaneous angiosarcoma
- primary cutaneous mucinous carcinoma

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THE DIAGNOSIS:

Metastatic Adenocarcinoma of the Colon

Cutaneous adenocarcinomas are uncommon, whether they present as a primary lesion or metastatic disease. In our patient, the histologic findings and immunohistochemical staining pattern were consistent with metastatic adenocarcinoma of the colon, an uncommon clinical presentation.

Colonic adenocarcinoma can cause cutaneous metastasis in 3% of cases. The most common sites of metastases include the abdomen, chest, and back.¹ On histologic examination, hematoxylin and eosin (H&E)-stained sections of cutaneous metastatic adenocarcinoma illustrate a malignant gland-forming neoplasm in the dermis with luminal mucin and necrotic debris (quiz image). The glands are lined by tall columnar epithelial cells with hyperchromatic nuclei. Alternatively, poorly differentiated morphology can be seen with fewer glands and more infiltrating nests of tumor cells.² Immunohistochemically, colonic adenocarcinoma typically is negative for cytokeratin (CK) 7 and positive for CK20 and caudal type homeobox transcription factor 2 (CDX-2).³

Primary cutaneous mucinous carcinoma is characterized by islands of neoplastic cells floating in pools of mucin (Figure 1). It may be indistinguishable from metastatic mucinous carcinomas of the colon or breast. Immunohistochemistry can be helpful in differentiating metastatic breast vs colon carcinoma. Cytokeratin 7, GATA binding protein 3, gross cystic disease fluid protein 15, and estrogen receptor will be positive in carcinomas of the breast and will be negative in colonic adenocarcinomas.⁴⁻⁶ Furthermore, lesional cells in metastatic adenocarcinoma of the colon are positive for CDX-2 and CK20, while those in metastatic carcinoma of the breast are negative.² Immunohistochemistry also can differentiate primary cutaneous carcinoma from metastatic adenocarcinoma. When used in combination, p63 and podoplanin (D2-40) offer a highly sensitive and specific indicator of a primary cutaneous neoplasm, as both demonstrate either focal or diffuse positivity in this setting. In contrast, these stains typically are negative in metastatic adenocarcinomas of the skin.⁷

Endometriosis affects 1% to 2% of all reproductive-age females, of which extrapelvic manifestations account for only 0.5% to 1.0% of cases.⁸ Histologically, extrapelvic endometriosis is characterized by the triad of endometrial-type glands, endometrial stroma, and hemorrhage or hemosiderin deposition (Figure 2). The glands can enlarge and demonstrate architectural distortion with partial lack of polarity. These features initially can be concerning for adenocarcinoma, but on closer examination, nuclear morphology is regular and mitoses are absent.^{8,9} The diagnosis usually can be rendered with H&E alone; however, immunohistochemical stains for CD10 and estrogen receptor can highlight the endometrial stroma.¹⁰ Furthermore,

endometrial glands will stain positive for paired box gene 8 (PAX8), a marker that is not expressed within the gastrointestinal tract and associated malignancies.¹¹

Primary cutaneous angiosarcoma may mimic adenocarcinoma, as the endothelial-lined vessels can be confused as malignant glands (Figure 3). Angiosarcoma often is seen in 1 of 3 clinical presentations: the head and neck of elderly patients, postradiation treatment, and chronic lymphedema.^{12,13} Regardless of the location, the disease carries a poor prognosis, with a 5-year survival rate of 12% following initial diagnosis.¹³ Angiosarcoma is characterized by malignant endothelial cells dissecting through the dermis. Although the histology can be deceptively bland in some cases, the neoplasm most commonly demonstrates notable atypia with a multilayered endothelium and occasional intravascular atypical cells (“fish in the

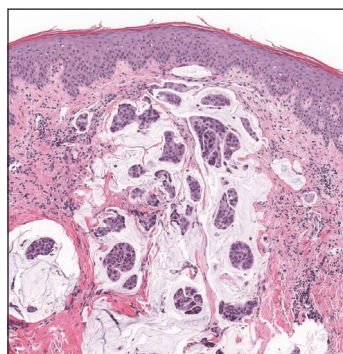


FIGURE 1. Primary cutaneous mucinous carcinoma. Pools of mucin are present within the dermis with islands of malignant tumor cells, ample cytoplasm, and nuclear pleomorphism (H&E, original magnification $\times 100$).

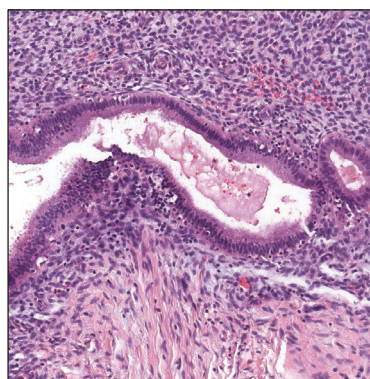


FIGURE 2. Endometriosis. An endometrial-type stroma is composed of bland-appearing spindle cells within the dermis with small interspersed capillaries and extravasated red blood cells. The glands are lined by columnar epithelial cells with regular, basally oriented nuclei and abundant cytoplasm (H&E, original magnification $\times 100$).

creek appearance”).^{13,14} There can be frequent mitoses, and the atypical cells may show intracytoplasmic lumina containing red blood cells. The lesional cells are positive for endothelial markers such as erythroblast transformation specific related gene (ERG), CD31, CD34, and friend leukemia integration factor 1 (FLI-1).^{15,16}

Breast cancer also can cause cutaneous metastases in approximately 20% of cases, with the most common presenting site being the anterior chest wall.¹⁷ Macroscopically, these lesions appear most commonly as painless nodules but also as telangiectatic, erysipeloid, fibrotic, and alopecic lesions.¹⁷⁻¹⁹ The histologic findings from H&E-stained sections of a cutaneous metastasis of breast cancer are variable and depend on the specific tumor subtype (eg, ductal, lobular, mucinous). However, the classic histologic presentation is that of nests and cords of malignant epithelial cells with variable gland formation. Often, tumor cells infiltrate in a single-file fashion (Figure 4).¹⁷ Although inflammatory breast carcinoma is a strictly clinical diagnosis, the presence of tumor cells in the lymphovascular spaces is a histologic clue to this diagnosis. Immunohistochemically, GATA binding protein 3 is helpful in identifying both hormone receptor–positive and –negative breast cancer subtypes that have metastasized.²⁰

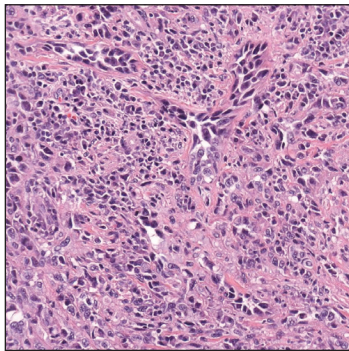


FIGURE 3. Primary cutaneous angiosarcoma. Large, atypical, pleomorphic cells line endothelial spaces and invade into the surrounding stroma. Occasionally, the vessels within angiosarcoma can mimic a gland-forming neoplasm (H&E, original magnification ×200).

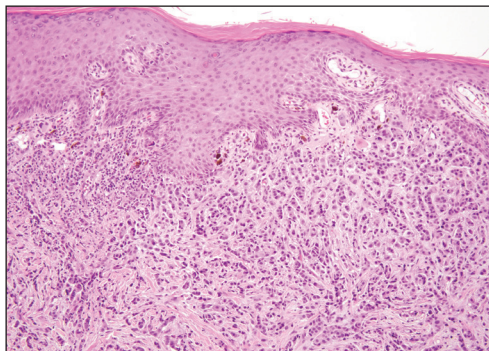


FIGURE 4. Metastatic breast carcinoma. Nests and cords of malignant epithelial cells are present within the dermis. Occasional tumor cells infiltrate in a single-file fashion (H&E, original magnification ×100).

Within the histologic differential diagnoses, the most useful tool to diagnose metastatic adenocarcinoma of the colon often is a thorough clinical history. In the absence of a clinical history of adenocarcinoma, immunohistochemistry can be a useful adjunct to aid in the correct characterization and classification of a malignant gland-forming tumor.^{2,3,6}

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