An enlarging painful nodule on the upper portion of the thigh

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CASE
An 87-year-old man was referred to dermatology with a 4-month history of a rapidly growing, painful, brown, 4.5×5.0-cm nodule on an erythematous base on his left thigh (Fig 1). He had experienced a dry cough in the preceding months and had a remote history of tobacco use and an occupation in manufacturing. Basic laboratory studies were unremarkable. An incisional biopsy, a histopathologic examination (Fig 2), and immunostainings were performed. The sample stained positive for thyroid transcription factor 1 (Fig 3), cytokeratin 7, and programmed death-ligand 1 (PD-L1) and nonreactive for CDX2, SOX10, NKX3.1, p40, synaptophysin, and cytokeratin 20. A positron emission tomography scan revealed a fluorodeoxyglucose-avid focus in the upper portion of the right lung and diffuse subcutaneous/lymphatic disease.

**Question 1: What is the most likely diagnosis?**

A. Pulmonary carcinoid tumor
B. Lung adenocarcinoma
C. Cutaneous tuberculosis
D. Mesothelioma
E. Lung squamous cell carcinoma

**Answers:**

A. Pulmonary carcinoid tumor — Incorrect. Though high-grade neuroendocrine tumors can express thyroid transcription factor 1, a nonreactive stain for synaptophysin makes this unlikely.1

B. Lung adenocarcinoma — Correct. Dual positivity with thyroid transcription factor 1 and cytokeratin 7 is highly specific and sensitive for primary adenocarcinoma of the lung.1 For this patient, a diagnosis of lung adenocarcinoma was made with histology alone prior to evidence of lung pathology from the positron emission tomography scan, and the nonreactivity of CDX2, SOX10, NKX3.1, p40, and synaptophysin narrowed the differential diagnosis due to the exclusion of the primaries of gastrointestinal, melanocytic, prostatic, squamous, and neuroendocrine origins, respectively.

C. Cutaneous tuberculosis — Incorrect. Though the clinical picture and positron emission tomography results can potentially be consistent with disseminated tuberculosis, the histology and immunohistochemistry results are most consistent with lung adenocarcinoma.1

D. Mesothelioma — Incorrect. Though the patient’s occupational history makes this an important diagnosis to consider, the histologic examination and immunostaining results are most consistent with lung adenocarcinoma.1

E. Lung squamous cell carcinoma — Incorrect. The critical marker for squamous cell carcinoma, p40, was negative, making this diagnosis unlikely.1

**Question 2: Which of the following is true about this case?**

A. Cutaneous metastases from lung adenocarcinoma are equally likely to present in all body sites
B. Immunohistochemistry results from distant metastatic sites can inform the selection of antineoplastic treatment
C. The presence of cutaneous metastases is a positive prognostic indicator of lung cancer
D. Lung adenocarcinoma is the most common cause of cutaneous metastases
E. Cutaneous metastases from lung adenocarcinoma usually present as multiple, grouped nodules

**Answers:**

A. Cutaneous metastases from lung adenocarcinoma are equally likely to present in all body sites — Incorrect. Lung cancer metastases usually present on the scalp, face, chest, abdomen, or back.2

B. Immunohistochemistry results from distant metastatic sites can inform the selection of antineoplastic treatment — Correct. PD-L1 expression can vary modestly by anatomic site and may be relatively upregulated in metastatic sites. However, patients with lung adenocarcinoma with high PD-L1 expression in metastatic site tissue demonstrate significantly increased progression-free survival on immune checkpoint inhibitors compared to those with negative PD-L1.3 Therefore, the assessment of cutaneous biopsies informs decisions regarding immune checkpoint inhibitors in the setting of lung adenocarcinoma as long as other therapy-driving markers (such as epithelial growth factor receptor) are also considered. Of note, the literature on metastases from other primaries is currently evolving, so this is not necessarily generalizable to other cancers.

C. The presence of cutaneous metastases is a positive prognostic indicator of lung cancer — Incorrect. The mean interval between the diagnosis...
of lung cancer and the development of cutaneous metastases is 16 months, ranging from concomitantly to 5 years. The interval from the recognition of cutaneous metastases to death is 3 to 6 months.

D. Lung adenocarcinoma is the most common cause of cutaneous metastases — Incorrect. Though lung cancer is the most common visceral source of cutaneous metastases in men, women more frequently experience skin involvement from breast cancer. To date, there have been case reports of lower-extremity cutaneous metastases from the following primaries, which, therefore, should be considered: bladder, colonic/rectal adenocarcinoma, breast carcinoma, non–small cell lung carcinoma, ovarian cancer, cervical cancer, prostate adenocarcinoma, oropharyngeal squamous cell carcinoma, pancreatic cancer, gallbladder cancer, endometrial cancer, and renal cell carcinoma.

E. Cutaneous metastases from lung adenocarcinoma usually present as multiple, grouped nodules — Incorrect. In one of the largest studies on cutaneous metastases to date, the majority of cutaneous metastases present at the time of diagnosis presented similarly to that in our patient, with a single nodule.

Question 3: What part of the body has the greatest predilection for cutaneous metastasis?

A. Anterior aspect of the torso
B. Posterior aspect of the torso
C. Upper extremities
D. Lower extremities
E. Pelvic region

Answers:
A. Anterior aspect of the torso — Correct. For women, the anterior aspect of the chest is the most common site of cutaneous metastasis; for men, it is the abdomen. The predilection for the anterior aspect of the chest wall in women may be due to the relatively high rates of breast cancer. Of note, the abdomen is the second-most common site for women.
B. Posterior aspect of the torso — Incorrect. Despite sharing approximately the same body surface area as the anterior torso, the posterior torso is one-fifth as common of a site as the anterior aspect of the torso.
C. Upper extremities — Incorrect. The upper extremities have not been shown to be a common site of cutaneous metastasis. When metastases do occur here, the most common primary is malignant melanoma.
D. Lower extremities — Incorrect. Although the lower extremities constitute over one-third of the body surface, this site accounts for only 4% of cutaneous metastases.
E. Pelvic region — Incorrect. Although not an uncommon site of cutaneous metastasis, the pelvic region is not the most common site. Carcinoma of the large intestines has been shown to be the most common primary tumor metastatic to this region.

Abbreviation used:
PD-L1: programmed death-ligand 1

Conflicts of interest
None disclosed.

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