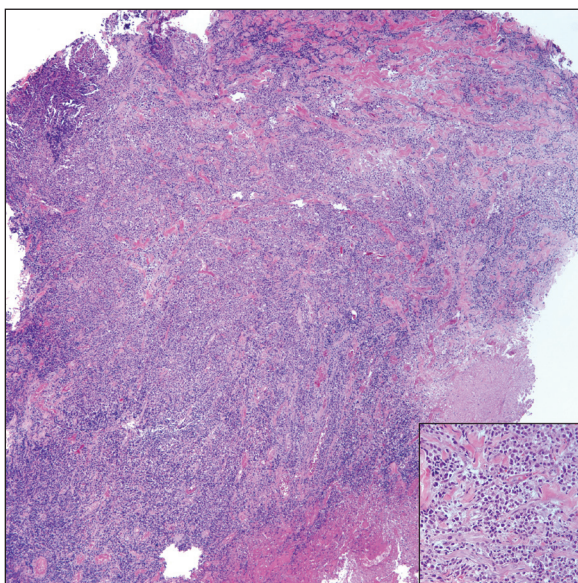


# Growing Nodule on the Arm

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H&E, original magnification  $\times 4$  (inset, original magnification  $\times 40$ ).

A 65-year-old white woman presented with an asymptomatic bump on the left upper arm of 4 months' duration that arose following a cat scratch. Physical examination was notable for a 35 $\times$ 30-mm, firm, ulcerated, exophytic nodule. Histologic examination demonstrated an ulcerated epidermis and a dense basophilic infiltrate occupying the entire dermis and extending to the subcutaneous tissue. Higher magnification (inset) demonstrated a pleomorphic population of medium- to large-sized discohesive round cells containing variable amounts of slightly eosinophilic cytoplasm, irregular nuclear contours, and prominent nucleoli. Scattered atypical mitotic figures were identified. CD30, CD4, leukocyte common antigen, and Ki-67 immunostains were strongly and diffusely positive. Notable negative stains included anaplastic lymphoma kinase, synaptophysin, epithelial membrane antigen, neuron-specific enolase, CD20, and S-100.

## THE BEST DIAGNOSIS IS:

- arthropod bite
- leukemia cutis
- Merkel cell carcinoma
- metastatic breast cancer
- primary cutaneous anaplastic large cell lymphoma

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The authors report no conflict of interest.

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## THE DIAGNOSIS:

## Primary Cutaneous Anaplastic Large Cell Lymphoma

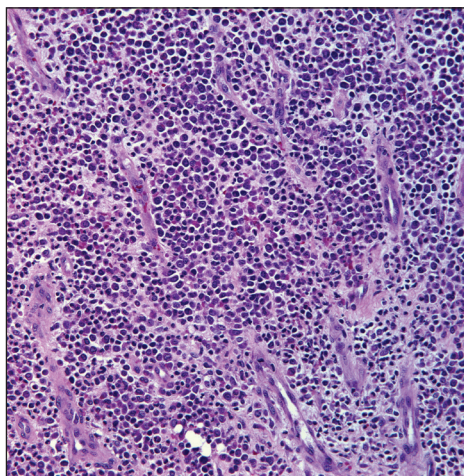
Primary cutaneous CD30<sup>+</sup> lymphoproliferative disorders encompass lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma (PCALCL) as well as borderline cases. Primary cutaneous anaplastic large cell lymphoma is a rare disease that is more common in white patients with slight male predominance and median age at diagnosis of 61 years.<sup>1</sup> Prognosis is excellent, with a 90% survival rate at 10 years. Although lesions spontaneously regress in 6% to 22% of cases, complete resolution is rare.<sup>2</sup> Clinically, the classic presentation is a solitary, rapidly growing, flesh-colored, erythematous nodule or plaque on the arms and legs or trunk, often with ulceration. Proper diagnosis requires clinical, histopathologic, and immunophenotypic correlation.

Histopathologic examination of PCALCL typically reveals large, atypical, Reed-Sternberg–like cells most commonly with anaplastic cytomorphology, but pleomorphic or immunoblastic morphology is not uncommon. Cells are in sheets or nodules, diffusely occupying the dermis and often the subcutaneous fat, with more than 75% of large cells expressing CD30.<sup>3</sup> In addition to CD30 positivity, immunophenotype is classically CD4<sup>+</sup>, cutaneous lymphocyte-associated antigen positive, epithelial membrane antigen negative, and anaplastic lymphoma kinase negative; CD2, CD5, and CD3 expression is variable. Interestingly, in our case, there was a minor population of CD8<sup>+</sup> cells. CD8 expression is seen in less than 5% of PCALCL cases; this phenotype is associated with an indolent disease with favorable prognosis.<sup>3</sup> Of note, anaplastic lymphoma kinase positivity corresponding to a t(2;5) translocation is more suggestive of systemic anaplastic large cell lymphoma with secondary skin involvement and more commonly is seen in children. For reasons possibly related to mediators such as epidermal growth factor or transforming growth factor  $\alpha$  from CD30<sup>+</sup> cells, epidermal hyperplasia can be seen in PCALCL.<sup>4</sup> The subsequent hyperkeratosis, crusting, and ulceration can be difficult to distinguish from lesions such as pyoderma gangrenosum, squamous cell carcinoma, arthropod bite, leukemia cutis, Merkel cell carcinoma (MCC), and metastatic breast cancer.

Skin involvement with leukemia is rare but most commonly is seen in acute myelogenous leukemia, specifically more mature forms such as acute myelomonocytic leukemia and acute monocytic leukemia. Approximately 10% to 20% of acute myelomonocytic leukemia cases have cutaneous involvement.<sup>5</sup> Although there is a variety of potential skin lesions, the most common is a red-purple papule or nodule, sometimes with hemorrhage or ulceration, on the head, neck, and trunk.

Leukemic infiltrates may arise from sites of prior trauma. Histopathology depends on the type of leukemia; however, general features include a normal epidermis without epidermotropism and perivascular, nodular, or diffuse infiltrate of neoplastic cells in the dermis, often with a Grenz zone (Figure 1). Compared to PCALCL, leukemia cutis shows sparing of the papillary dermis (Grenz zone), and the cells have more cytoplasm and show a different immunophenotype. The cells often are fragile and show crush artifact. Acute myelogenous leukemia often will show cytoplasmic granules; however, immature precursor cells may not have granules. The myeloid cells will stain with myeloperoxidase and chloroacetate. Positivity is seen for CD13, CD33, and CD68. Clinical correlation is important because other diseases with nodular or diffuse infiltrates of small cell infiltrates, such as extramedullary hematopoiesis and lymphoma, appear similar. Acute myelogenous leukemia is associated with neutrophilic dermatoses such as Sweet syndrome and pyoderma gangrenosum. Cutaneous eruption resolves with successful treatment of the leukemia.

Breast cancer is the most common cancer to metastasize to the skin in women, accounting for 73% of cutaneous metastases, followed by melanoma, which is responsible for 11%.<sup>5</sup> The classic presentation is an erythematous patch with spreading borders or a nodule on the trunk. Many cases of metastatic breast cancer with skin involvement may represent direct extension of the cancer into the skin. General histologic clues to cutaneous

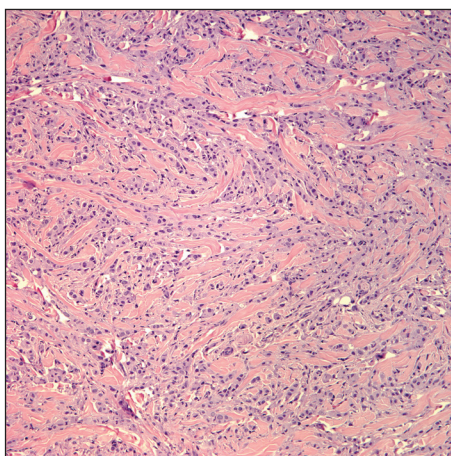


**FIGURE 1.** Diffuse infiltrate of monotonous large cell population with high nuclear to cytoplasmic ratio in the setting of myeloid-type leukemia cutis. Cells are round with slightly irregular nuclear contours, finely dispersed chromatin, and prominent nucleoli (H&E, original magnification  $\times 20$ ).

metastasis include well-circumscribed dermal or subcutaneous nodules of atypical cells with an increase in mitotic activity without connection to the epidermis. Tumor cells may show diffuse, nodular, or single file pattern and may exhibit areas of necrosis. Ductal carcinoma additionally may show ductal or glandular differentiation with surrounding desmoplasia (Figure 2). Immunohistochemistry typically is positive for cytokeratin (CK) 7, estrogen receptor/progesterone receptor, mammaglobin, and gross cystic disease fluid protein-15, and negative for CK20, CK5/6, and thyroid transcription factor-1.

Papulovesicular and nodular lesions appearing as an arthropod bite have been noted in hematologic malignancies, underscoring the importance of histopathology and clinical correlation. Arthropod bites commonly present as red papules, nodules, vesicles, or pustules at the site of the bite. Pseudolymphomatous nodules occasionally develop. Excoriations and further progression to persistent prurigo also may occur. Histopathology shows variable epidermal features including spongiosis, acanthosis, parakeratosis, dermal edema, and superficial and deep perivascular neutrophils (Figure 3). Additionally, lymphocytes sometimes with CD30 positivity may be seen. The presence of eosinophils in interstitial areas, especially in the deep dermis, is a useful clue.

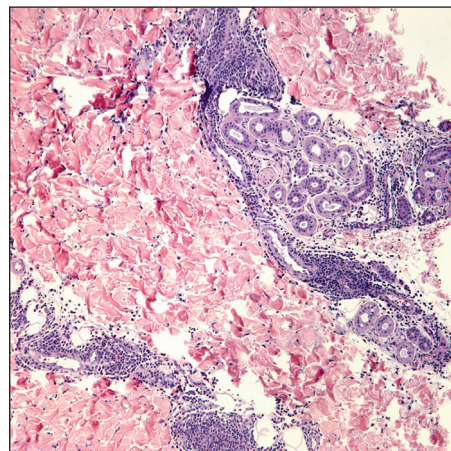
Lack of staining for epithelial and neuroendocrine markers differentiates PCALCL from MCC; specifically CK20, an epithelial marker positive in more than 90% of MCC cases, excludes lymphoma.<sup>6</sup> Merkel cell carcinoma presents as a solitary, quickly growing, red and often ulcerated nodule or plaque on the head, neck, or legs of elderly patients. The lesions often are in areas of sun damage. Histopathology classically shows a diffuse dermal infiltrate of monotonous round blue cells with a scant cytoplasmic rim and multiple inconspicuous nucleoli in nests, rosettes, or strands in the dermis. There are frequent



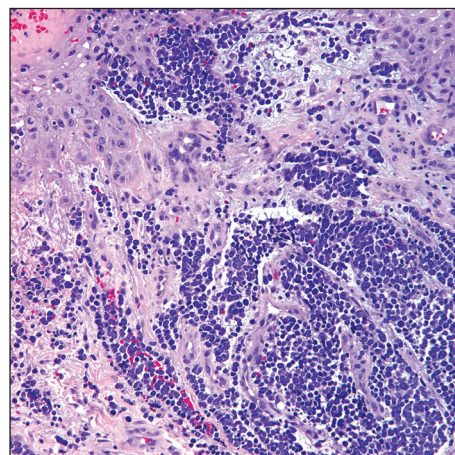
**FIGURE 2.** Cutaneous metastatic invasive ductal adenocarcinoma of the breast exhibits cords of cohesive pleomorphic epithelioid cells invading the dermis with apparent desmoplastic reaction (H&E, original magnification  $\times 10$ ).

mitotic figures. The cells are uniform and 2 to 3 times larger than mature lymphocytes. Single-cell necrosis and crush artifact is common. Epidermotropism or coexisting Bowenoid change also may be observed (Figure 4). The term *primary neuroendocrine carcinoma of the skin* is preferred over *Merkel cell carcinoma* because the tumor cells share similar morphology to the specialized touch receptor of the basal layer (Merkel cell), but no direct histogenetic relationship has been established.<sup>7,8</sup>

Immunohistochemistry is key to diagnosis because MCC stains for both epithelial and neuroendocrine markers. Positivity is seen for neuron-specific enolase, epithelial membrane antigen, neurofilament, synaptophysin,



**FIGURE 3.** Perivascular mixed inflammatory infiltrate composed of lymphocytes, histiocytes, eosinophils, and neutrophils in the setting of an arthropod bite (H&E, original magnification  $\times 10$ ).



**FIGURE 4.** Nodular infiltrate of monotonous small cells in Merkel cell carcinoma can appear hematopoietic, necessitating neuroendocrine and epithelial stains. Tumor cells have scant cytoplasm, vesicular nuclei with finely granular and dusty chromatin, single cell apoptosis, and frequent mitoses (H&E, original magnification  $\times 20$ ).

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and chromogranin. Because the histology of MCC may resemble small cell carcinoma of the lung, staining for low-molecular-weight keratin such as CK20 and CK7 help to distinguish MCC. Merkel cell carcinoma typically is CK20<sup>+</sup> and CK7<sup>-</sup>, while small cell carcinoma of the lung is the opposite.<sup>9</sup> The tumor grows aggressively and metastasis is common, thus surgery is the primary approach, but adjuvant chemotherapy and radiation often are given in addition.

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