Painful Growing Nodule on the Right Calf

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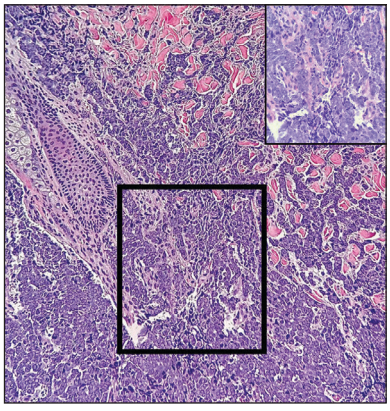
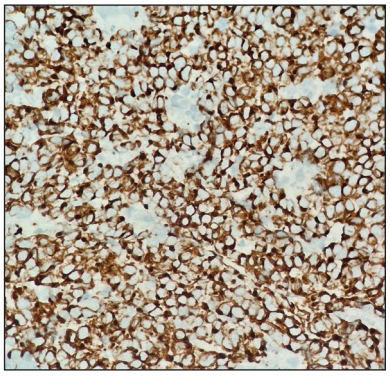


H&E, original magnification ×100 (inset: H&E, original magnification ×400).



Cytokeratin 20, original magnification ×400.

A 47-year-old woman with a history of combined variable immunodeficiency presented with a 2.6×2.4-cm nodule on the lateral aspect of the right calf that was first noticed 2 years prior as a smaller nodule. It increased in size and became painful to touch over the last 3 to 4 months. Following diagnostic biopsy, the nodule was removed by wide local excision and was tan-brown on gross dissection. The lesion showed dotlike perinuclear positivity with cytokeratin 20 immunostaining. Positron emission tomography–computed tomography showed no evidence of lung lesions. A complete blood cell count was within reference range.

THE BEST **DIAGNOSIS IS:**

a. basal cell carcinoma, infiltrative type
b. leukemia cutis
c. Merkel cell carcinoma
d. metastatic small cell carcinoma
e. small cell melanoma

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THE **DIAGNOSIS:** Merkel Cell Carcinoma

Multiple diagnoses should be considered for a small, round, blue cell neoplasm of the skin, including both primary and metastatic entities. In our patient, histopathology revealed sheets and nests of infiltrative neoplastic cells with dispersed chromatin, minimal cytoplasm, and multiple mitoses (quiz image 1).[1] The lesional cells were in the dermis and superficial subcutaneous tissue but did not appear to be arising from the epidermis. Lymphovascular invasion also was evident on additional sections. Metastatic disease was identified in 3 sentinel lymph nodes from the right inguinal and right iliac regions. These features were compatible with a diagnosis of Merkel cell carcinoma (MCC).

Merkel cell carcinoma is a rare malignant neuroendocrine cutaneous tumor with a worldwide incidence of 0.1 to 1.6 cases per 100,000 individuals annually.[2] The typical patient is older than 75 years with fair skin and a history of extensive sun exposure. Immunocompromised individuals are predisposed and more susceptible to infection with the Merkel cell polyomavirus, which promotes oncogenesis in the majority of MCCs. Our patient's history of combined variable immunodeficiency likely explains her presentation at a younger age.

The prognosis in patients with MCC is poor, with 5-year survival rates of 51% for local disease, 35% for nodal disease, and 14% for systemic metastases. Survival also is reduced in cases with head/neck primary tumors and polyomavirus-negative tumors, as well as in immunocompromised patients.[2] Treatment of resectable MCC consists of Mohs micrographic surgery or wide local excision depending on the patient's cosmetic concerns. Radiation therapy is recommended for cases with increased risk for recurrence or positive surgical margins, as well as when additional resection is impossible. A study investigating immunotherapy with nivolumab demonstrated complete pathologic response and radiographic tumor regression in nearly half of patients when given 4 weeks prior to surgery.[3]

Immunohistochemistry is essential in discerning MCC from other small blue cell tumors. Most MCC cases show positive expression of neuroendocrine markers such as synaptophysin, chromogranin, and insulinoma-associated protein 1. Perinuclear dotlike staining with cytokeratin (CK) 20 (quiz image 2) commonly is seen, but up to 15% of cases may be CK20 negative. Many of these CK20-negative cases also express CK7. This tumor also may stain with paired box 5 (PAX-5), CD99, terminal deoxynucleotidyl transferase, Ber-EP4, and CD117[1,4]; melanoma stains (ie, human melanoma black [HMB] 45, SRY-related HMB-box 10 [SOX-10], S-100, melanoma antigen recognized by T-cells 1 [MART-1]) should be negative. However, PAX-5 expression may be a potential pitfall given that B-cell lymphomas also would express that marker and could mimic MCC histologically. Therefore, other universal lymphoid markers such as CD45 should be ordered to rule out this entity. Even with one or a few aberrant stains, a diagnosis of MCC still can be rendered using the histomorphology and the overall staining profile.[4] Of prognostic significance, p63 expression is associated with more aggressive tumors, while Bcl-2 expression is favorable, as it offers an additional targeted treatment option.[5,6]

Basal cell carcinoma (BCC) is linked to excessive sun exposure and is the most common skin cancer. Similar to MCC, it typically is mitotically active and hyperchromatic; however, lymphovascular invasion or metastasis almost never is observed in BCC, whereas approximately one-third of MCC cases have metastasized by the time of diagnosis. Additionally, BCC lacks the perinuclear dotlike staining seen with CK20.[2,7] Features present in BCC that are unusual for MCC include peripheral nuclear palisading, mucin, and retraction artifact on paraffin-embedded sections (Figure 1).[7]

Leukemia cutis (or cutaneous infiltrates of leukemia) commonly displays a perivascular and periadnexal pattern in the dermis and subcutis. These infiltrates of neoplastic leukocytes can congregate into sheets, sometimes with an overlying Grenz zone, or form single-file infiltrates (Figure 2).[1,4] The neoplastic cells can be monomorphic or atypical and commonly are susceptible to crush artifact.[4] Although the immunohistochemical profile

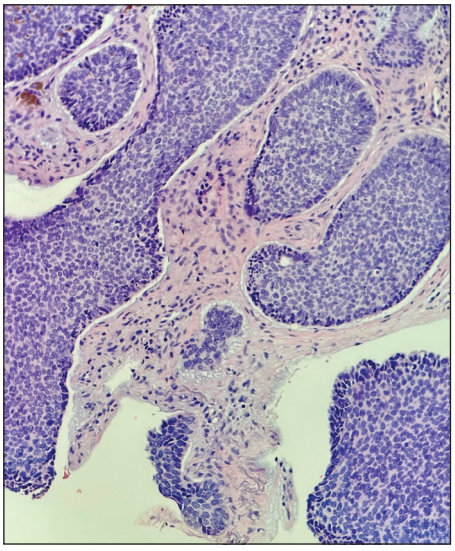

FIGURE 1. Basal cell carcinoma. Nodular growth with classic peripheral nuclear palisading, retraction, and focal mucin (H&E, original magnification ×200).

varies depending on the etiology of the underlying leukemia, broad hematologic markers such as CD43 and CD45 are helpful to discern these malignancies from MCC.[4]

Being neuroendocrine in origin, metastatic small cell carcinoma (Figure 3) strongly mimics MCC histologically and usually stains with synaptophysin, chromogranin, and insulinoma-associated protein 1. Both tumor cells typically exhibit nuclear molding and high mitotic rates. Although small cell carcinoma is more likely to stain with high-molecular-weight cytokeratins (ie, CK7), it is not uncommon for these tumors to express low-molecular-weight cytokeratins such as CK20. Because most cases originate from the lungs, these lesions

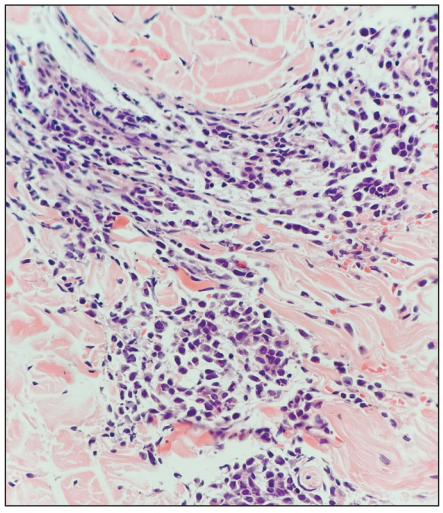

FIGURE 2. Leukemia cutis. Infiltration of metastatic leukemia cells in the dermis with a single-file infiltration pattern and atypical nuclei (H&E, original magnification ×400).

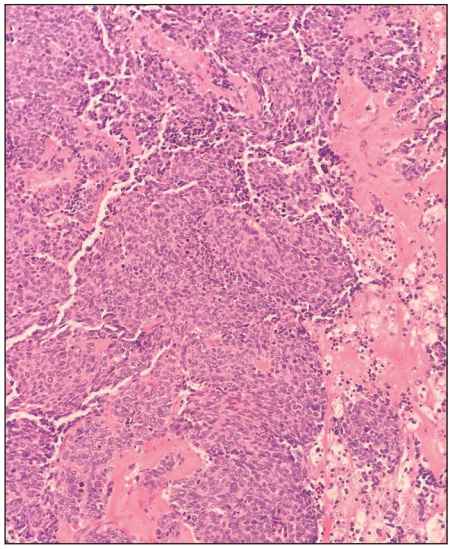

FIGURE 3. Metastatic small cell carcinoma. Sheets of infiltrative basophilic cells with fine chromatin, nuclear molding, and brisk mitoses (H&E, original magnification ×200).

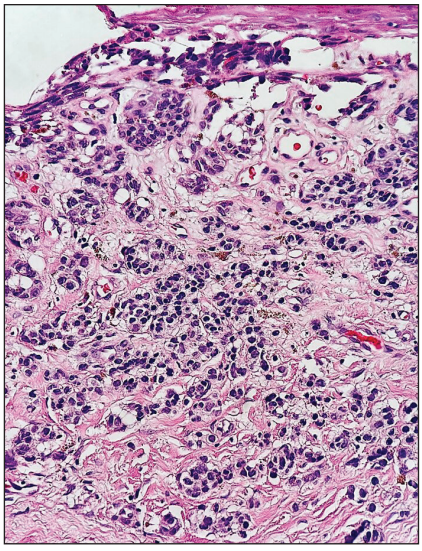

FIGURE 4. Small cell melanoma. Infiltrative nests and individual cells involving the epidermis and dermis (H&E, original magnification ×400).

should be positive for thyroid transcription factor 1 and negative for PAX-5, whereas MCC would show the reverse for those stains.[1] Ultimately, however, clinical correlation with imaging results is the single best methodology for differentiation.

Small cell melanoma, a variant of nevoid melanoma, can strongly resemble an MCC or a lymphoma. Usually located on the scalp or arising from a congenital nevus, small cell melanomas are aggressive and confer an unfavorable prognosis. Histologically, they consist of nests to sheets of atypical cells within the epidermis and dermis. These cells typically exhibit hyperchromatic nuclei, minimal cytoplasm, and frequent mitoses (Figure 4). Furthermore, the cells do not display maturation based on depth.[8] These tumors usually are positive for HMB45, S-100, MART-1, SOX-10, and tyrosinase, all of which are extremely unlikely to stain an MCC.[1]

REFERENCES

1. Patterson JW, Hosler GA. *Weedon's Skin Pathology*. 4th ed. Churchill Livingstone/Elsevier; 2016.
2. Walsh NM, Cerroni L. Merkel cell carcinoma: a review. *J Cutan Pathol*. 2021;48:411-421.
3. Topalian SL, Bhatia S, Amin A, et al. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 Trial. *J Clin Oncol*. 2020;38:2476-2488.
4. Rapini RP. *Practical Dermatopathology*. 3rd ed. Elsevier; 2021.
5. Asioli S, Righi A, Volante M, et al. p63 expression as a new prognostic marker in Merkel cell carcinoma. *Cancer*. 2007;110:640-647.
6. Verhaegen ME, Mangelberger D, Weick JW, et al. Merkel cell carcinoma dependence on Bcl-2 family members for survival. *J Invest Dermatol*. 2014;134:2241-2250.
7. Le MD, O'Steen LH, Cassarino DS. A rare case of CK20/CK7 double negative Merkel cell carcinoma. *Am J Dermatopathol*. 2017;39:208-211.
8. North JP, Bastian BC, Lazar AJ. Melanoma. In: Calonje E, Brenn T, Lazar AJ, et al, eds. *McKee's Pathology of the Skin With Clinical Correlations*. 5th ed. Elsevier; 2020.