

Erythematous Nodular Plaque Encircling the Lower Leg

What's the diagnosis?



A 66-year-old woman presented with red to violaceous, rapidly growing nodules on the skin. Her medical history was remarkable for diabetes mellitus, hypertension, dyslipidemia, and renal failure. She had 2 rejected kidney transplants and was on hemodialysis at the time of presentation. She noticed asymptomatic nodules present on the left lower leg that progressively coalesced, finally encroaching the whole girth of the limb, spreading from the foot to the knee in a short duration of 3 months. The regional lymph nodes were not clinically palpable.

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The authors report no conflict of interest.

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The Diagnosis: Merkel Cell Carcinoma

Histopathology showed small round cells (Figure 1) that stained positive for cytokeratin 20 in a paranuclear dotlike pattern (Figure 2). The tumor stained negative for lymphoma (CD45) marker. Fluorodeoxyglucose positron emission tomography showed focally increased activity at cutaneous sites corresponding to the nodules, but lymph nodes and visceral sites did not show areas of increased metabolic activity. She underwent an above-knee amputation. She was started on a chemotherapy regimen of etoposide and carboplatin given that the pathology of the excised limb demonstrated vascular and lymphatic invasion by the tumor cells in the proximal skin margin. After 4 months she presented with gangrenous changes of the amputated limb and evidence of metastasis to the region of the skin flap. Similar tumors presented on the ipsilateral hip. Given her general poor condition and aggressive nature of the tumor, the patient decided to pursue hospice care 6 months after her diagnosis of Merkel cell carcinoma (MCC).

Merkel cell carcinoma usually presents as firm, red to purple papules on sun-exposed skin in older patients with light skin. Factors strongly associated with the development of MCC are age (>65 years), lighter skin types, history of extensive sun exposure, and chronic immune suppression (eg, kidney or heart transplantation, human immunodeficiency virus).¹ The rate of MCC has

increased 3-fold between 1986 and 2001; the rate of MCC was 0.15 cases per 100,000 individuals in 1986, climbing up to 0.44 cases per 100,000 individuals in 2001.² Our patient had been on immunosuppressants—prednisone, cyclosporine, and sirolimus—for nearly a decade following kidney transplants, which had been discontinued 2 years prior to presentation.

Heath et al³ defined an acronym AEIOU (asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than 50 years, UV-exposed site on a person with fair skin) for MCC features derived from 195 patients. They advised that a biopsy is warranted if the patient presents with more than 3 of these features.³

The 1991 MCC staging system was revised in 1999 and 2005 based on experience at Memorial Sloan Kettering Cancer Center (New York, New York).⁴ In 2010 the American Joint Committee on Cancer staging was introduced for MCC, which follows other skin malignancies.⁵ Using this TNM staging system for primary tumors, regional lymph nodes, and distant metastasis, our patient at the time of presentation was stage IIB (T3N0M0), with tumor size greater than 5 cm, nodes negative by clinical examination, and no distant metastasis. In a span of 3 months, she had metastasis to the skin, subcutaneous tissue, and distant lymph nodes, which resulted in classification as stage IV, proving the aggressive nature of the tumor.

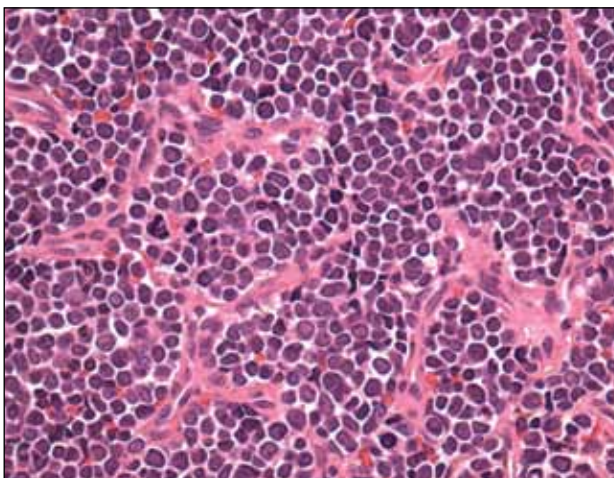


Figure 1. The tumor was composed of sheets of cells with a high nuclear-cytoplasmic ratio and fine chromatin without nucleoli (H&E, original magnification $\times 40$).

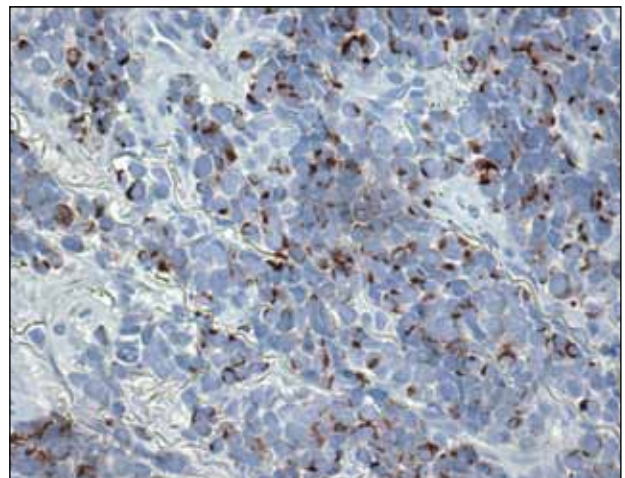


Figure 2. Immunohistochemical staining for cytokeratin 20 showed positivity in a paranuclear dotlike pattern (original magnification $\times 40$).

The newly discovered Merkel cell polyomavirus (MCPyV) is found integrating into the Merkel cell genome. Merkel cell polyomavirus is present in 80% of cancers and is expressed in a clonal pattern, while 90% of MCC patients are seropositive for the same. Unlike antibodies to MCPyV VP1 protein, antibodies to the T antigen for MCPyV track disease burden and may be a useful biomarker for MCC in the future.⁶

A study of 251 patients in 1970-2002 showed that pathologic nodal staging identifies a group of patients with excellent long-term survival.¹ Our patient preferred to undergo positron emission tomography rather than a sentinel lymph node biopsy prior to surgery. Also, after margin-negative excision and pathologic nodal staging, local and nodal recurrence rates were low. Adjuvant chemotherapy for stage III patients showed a trend ($P=.08$) to decreased survival compared with stage II patients who did not receive chemotherapy.⁷ A multidisciplinary approach to treatment including surgery, radiation,⁸ and chemotherapy needs to be created for each individual patient. Merkel cell carcinoma is the cause of death in 35% of patients within 3 years of diagnosis.⁹

Merkel cell carcinoma is a rare orphan tumor with rapidly increasing incidence in an era of immunosuppression. It has a grave prognosis, as demonstrated in our case, if not detected early. People at increased risk for MCC must have regular skin checks. Unfortunately, our patient was a nursing home resident and had not had a skin check for 2 years prior to presentation.

REFERENCES

1. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol*. 2005;23:2300-2309.
2. Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol*. 2005;89:1-4.
3. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol*. 2008;58:375-381.
4. Edge S, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*. New York, NY: Springer; 2010.
5. Assouline A, Tai P, Joseph K, et al. Merkel cell carcinoma of skin-current controversies and recommendations. *Rare Tumors*. 2011;4:e23.
6. Paulson KG, Carter JJ, Johnson LG, et al. Antibodies to Merkel cell polyomavirus T-antigen oncoproteins reflect tumor burden in Merkel cell carcinoma patients. *Cancer Res*. 2010;70:8388-8397.
7. Poulsen M, Rischin D, Walpole E, et al; Trans-Tasman Radiation Oncology Group. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study—TROG 96:07. *J Clin Oncol*. 2003;21:4371-4376.
8. Lewis KG, Weinstock MA, Weaver AL, et al. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol*. 2006;142:693-700.
9. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. *J Am Acad Dermatol*. 2003;49:832-841.