

# Merkel Cell Carcinoma: Case Report

Blakely Richardson, DO; Lyubov Avshalumova, DO; Richard Miller, DO

*Merkel cell carcinoma (MCC), also termed cutaneous small cell carcinoma or trabecular carcinoma, is a rare tumor that most often presents as a solitary nodule on the head, neck, or extremities of older adults. It is an aggressive tumor that usually is fatal due to rapid metastasis. Involvement of lymph nodes at presentation can be used to predict survival. Because MCC is sensitive to radiation, it can be used as an adjunct to surgery. We report a case of MCC to alert clinicians of this potentially fatal tumor because early diagnosis and proper treatment may improve patient survival rates.*

*Cutis.* 2011;88:296-299.

## Case Report

An 88-year-old woman was referred to the dermatology office with 2 large growing lesions on the right cheek that had been present for 6 weeks. The patient resided in a nursing home and had the lesions biopsied in the past. However, the lesions grew back within a couple of weeks. Her medical history was remarkable for diabetes mellitus and basal cell carcinoma of the face.

Skin examination revealed 2 erythematous painless firm nodules with central ulceration, each measuring approximately 4 cm in diameter, present on the right distal cheek. Both lesions were biopsied at the patient's nursing home. A biopsy of the superior lesion was consistent with nodular basal cell carcinoma. The inferior nodule, however, was consistent with a neuroendocrine carcinoma with tumor cells showing paranuclear dot of positivity with pancytokeratin and cytokeratin 20 (CK20). Lesional cells were highlighted with synaptophysin. Leukocyte common antigen and S-100 stains were negative, ruling out cutaneous lymphoma and melanoma,

respectively. The differential diagnosis included Merkel cell carcinoma (MCC) and metastatic small cell carcinoma.

Wide primary excision down to fascia was performed on the day of the visit. Histopathologic examination was consistent with poorly differentiated invasive carcinoma with neuroendocrine differentiation consistent with MCC (Figures 1 and 2). Cells had dotlike CK20 (Figure 3), synaptophysin, and cytokeratin 903 positivity. Cytokeratin 7 and thyroid transcription factor-1 immunohistochemical stains were negative; these stains play an important role in differentiating metastatic small cell lung cancer and MCC. Cytokeratin 20 is a specific immunophenotypic marker for Merkel cells that is commonly found in MCC and stains in a characteristic dotlike pattern.<sup>1</sup> Cytokeratin 20, however, is rarely ever found in small cell lung cancer. Thyroid transcription factor-1 is found in follicular cells of the thyroid as well as alveolar type II epithelial cells and in subsets of nonciliated bronchiolar epithelial cells in the lung. It is commonly found in small cell lung carcinoma but is negative in MCC.<sup>1</sup>

The patient was referred to oncology and started on adjuvant radiation therapy with a prescribed course of 5940 cGy. The patient refused sentinel node biopsy or node dissection. At the follow-up visit, we were informed that the patient had an ultrasound-guided biopsy of a right breast mass that was seen on positron emission tomography as well as a right axillary mass, which was consistent with grade 2 invasive ductal carcinoma of the breast. The lesion was found to be estrogen receptor positive and the patient was started on anastrozole; she refused concurrent chemotherapy for her MCC. Excision sites, however, appeared clear of recurrences and the patient finished her prescribed course of salvage radiotherapy.

## Comment

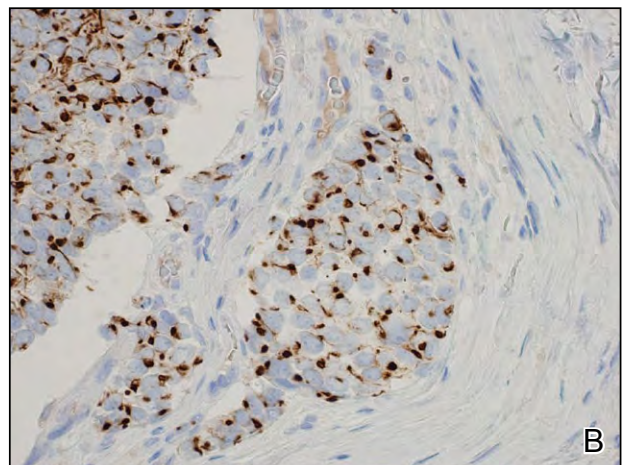
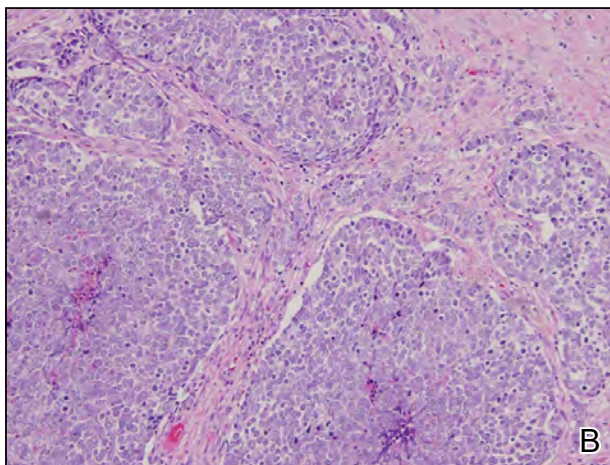
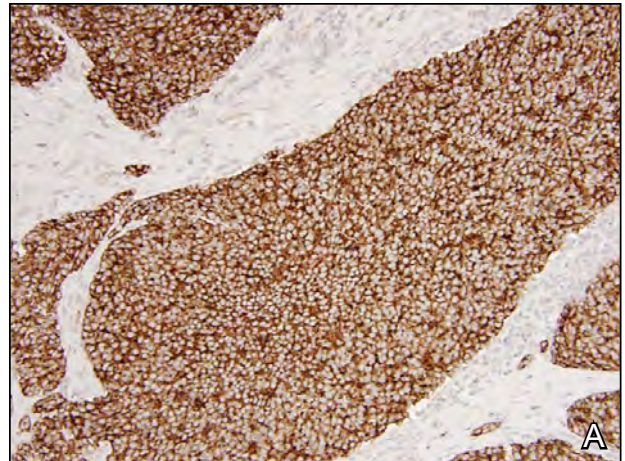
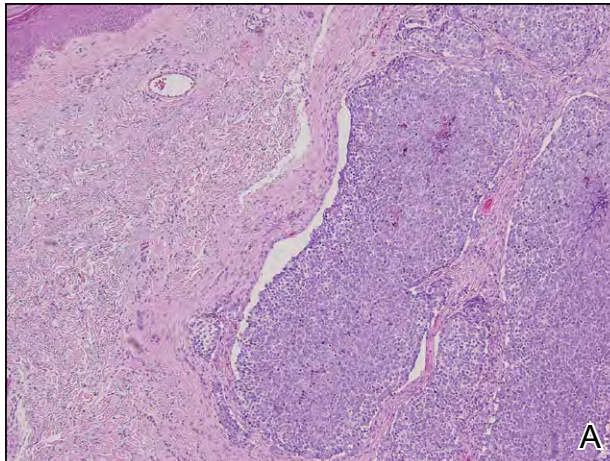
Merkel cells are neuroendocrine cutaneous cells found in the basal cell layer of the epidermis.<sup>2</sup> Merkel cells are highly concentrated in the touch-sensitive areas, such as the glabrous regions, but also are found in hairy areas as well as mucosal surfaces. Their

---

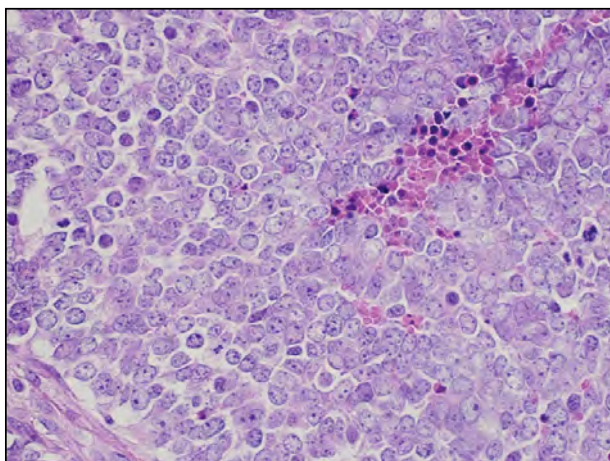
Dr. Richardson is from University Hospitals Case Medical Center, Cleveland, Ohio. Drs. Avshalumova and Miller are from Largo Medical Center, Florida.

The authors report no conflict of interest.

Correspondence: Blakely Richardson, DO, Department of Dermatology, 11100 Euclid Ave, Cleveland, OH 44106 (blakely.richardson@uhhospitals.org).



**Figure 1.** Collection of atypical small blue cells (A and B) (H&E; original magnifications  $\times 10$  and  $\times 20$ , respectively).



**Figure 2.** High-power view showing central clearing of nuclei, multiple nucleoli, apoptotic cells, and mitotic figures (H&E, original magnification  $\times 40$ ).

specific function has not been identified, but their close association with nerve fibers and their ability to secrete an array of peptides suggest they may have a role in skin homeostasis and cutaneous nerve

**Figure 3.** Cytokeratin 20–positive staining, with high-power view demonstrating brown paranuclear dots (A and B)(original magnifications  $\times 20$  and  $\times 40$ , respectively).

development.<sup>2</sup> Merkel cells were believed to be derived from neural crest cells, which migrate to their location during embryogenesis. However, more recent evidence may point to an epithelioid precursor.<sup>3</sup>

Once believed to be a benign skin tumor, MCC is a rare and highly aggressive malignant tumor arising from Merkel cells in the dermoepidermal junction. Merkel cell carcinoma was first described by Toker<sup>4</sup> in 1972 as a malignant trabecular neoplasm, and in 1978, Tang and Toker<sup>5</sup> demonstrated the presence of dense granules within the tumor. Merkel cell carcinoma usually presents as a painless, rapidly growing, solitary, violaceous, dome-shaped, indurated nodule that occurs most commonly on sun-exposed areas, such as the head and neck. This tumor is most common in the elderly population with a mean age of 68 years. Merkel cell carcinoma also has been reported following radiation and immunosuppressive therapy as well as in conjunction with other malignancies.<sup>6</sup> Recently, MCC has been linked to a *Polyomavirus*, now termed *Merkel cell polyomavirus* (MCV). A study by Feng et al<sup>7</sup> demonstrated that viral DNA was integrated

into the tumor genome in 6 of 8 MCV-positive MCCs. Therefore, MCV may be a contributing factor in the oncogenesis of MCC.<sup>7,8</sup>

On microscopic examination, the tumor resides in the dermis and infiltrates the subcutaneous tissue. There is a dense proliferation of small dark cells that demonstrate neuroendocrine differentiation.<sup>5</sup> A considerable number of cases have demonstrated bowenoid changes in the epidermis as well as basal and squamous differentiation. Some cases also have demonstrated positive epithelial markers, thus supporting the proposed epithelial origin of MCC.<sup>2</sup> However, these bowenoid changes also may represent coincidental squamous cell carcinoma in sun-damaged skin.

It often is difficult to distinguish MCC from metastatic tumors with similar histologic features such as small cell lung cancer or other neuroendocrine tumors from other sites. Staining for CK20 may help differentiate MCC from other neuroendocrine tumors.<sup>5,9</sup> Electron microscopy reveals dense granules and paranuclear fibrous bodies, distinguishing MCC from metastatic small cell carcinoma.<sup>5</sup>

In a study conducted by Skelton et al,<sup>3</sup> the most remarkable histologic feature correlating to increased mortality was cell size. The small cell variants resembling lymphoid cells were associated with a higher incidence of death, while the intermediate cell type offered a better prognosis.<sup>3</sup> Other poor prognostic factors include tumor size greater than 2 cm, mitotic rate greater than 10 per high-power field, and nodal and systemic metastasis.<sup>2,5</sup> It has been suggested that the evidence of ulceration may be an indicator that metastasis has occurred.<sup>10</sup> However, more studies are needed to evaluate this claim.

Although rare, with 400 cases annually documented in the United States, MCC proves to be more fatal than any other skin malignancy, with a mortality rate of approximately 25%, and a high incidence of recurrence. Because of the inability to conduct large randomized trials, defining standards for optimal therapy has proved to be challenging.<sup>5,11</sup> Surgery is the mainstay of treatment calling for wide local excision with 2- to 3-cm margins. Locoregional recurrence ranges from 20% to 75%. Radiation therapy has been used as an adjunct and for recurrent tumors; it offers improved locoregional control. Chemotherapy, however, has principally been used for palliative management in severe disease.<sup>5</sup> There have been debates over the recommendation for lymph node dissection as well as sentinel node biopsy. A study by Gupta et al<sup>12</sup> has shown that sentinel node biopsy may detect clinically understaged disease and permit direct removal of positive nodes, leading to better outcome. Allen et al<sup>13</sup> also found that pathologic nodal staging was associated with improved stage-specific survival and

decreased nodal recurrence. These data have led some institutions to advocate a multimodal approach with wide primary excision, adjuvant radiation to both the primary site and draining lymph nodes, and lymph biopsy as the best initial treatment of MCC.<sup>12,13</sup> Studies also have found that local control rates range from 60% to 90% for combined modality treatment including surgery plus radiation therapy.<sup>13-23</sup> As part of a multimodality approach, adjuvant radiation therapy has improved survival outcomes with 5-year survival rates of 60% to 80%.<sup>24</sup>

Merkel cell carcinoma is so rare that it has been difficult to assess prognostic features and determine standards of treatment. Immunohistochemical staining has made the diagnosis of MCC more accurate. Currently, disease stage as well as tumor architecture, thickness, and lymphovascular invasion are considered independent predictors of survival. However, more histologic data are needed to determine significance of these findings.<sup>25</sup> Progress is being made through pooling of data of chromosome analysis to determine what chromosomal aberrations are involved in MCC and determine its aggressiveness.<sup>12</sup> With this information, future studies may eventually help improve treatment plans and outcomes.

## REFERENCES

- Bobos M, Hytiroglou P, Kostopoulos I, et al. Immunohistochemical distinction between merkel cell carcinoma and small cell carcinoma of the lung. *Am J Dermatopathol*. 2006;28:99-104.
- Boulais N, Misery L. Merkel cells [published online ahead of print April 6, 2007]. *J Am Acad Dermatol*. 2007;57:147-165.
- Skelton HG, Smith KJ, Hitchcock CL, et al. Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. *J Am Acad Dermatol*. 1997;37(5, pt 1):734-739.
- Toker C. Trabecular carcinoma of the skin. *Arch Dermatol*. 1972;105:107-110.
- Tang CK, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. *Cancer*. 1978;42:2311-2321.
- Akhtar S, Oza KK, Wright J. Merkel cell carcinoma: report of 10 cases and review of the literature. *J Am Acad Dermatol*. 2000;43(5, pt 1):755-767.
- Feng H, Shuda M, Chang Y, et al. Clonal integration of a polyomavirus in human Merkel cell carcinoma [published online ahead of print January 17, 2008]. *Science*. 2008;319:1096-1100.
- Kreuter A. A new polyomavirus linked to Merkel cell carcinoma. *Arch Dermatol*. 2008;144:1393.
- Nandedkar MA, Patterson RH, Bridgeman-Shah S, et al. A large friable tumor overlying the left side of the mandible—case. *Arch Dermatol*. 2004;140:609-614.
- Lowry F. Merkel cell ulceration may indicate metastasis. *Skin & Allergy News*. 2007;38:16.

11. Herbst A, Haynes HA, Nghiem P. The standard of care for Merkel cell carcinoma should include adjuvant radiation and lymph node surgery. *J Am Acad Dermatol.* 2002;46:640-642.
12. Gupta SG, Wang LC, Peñas PH, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol.* 2006;142:685-690.
13. 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.
14. Boyer JD, Zitelli JA, Brodland DG, et al. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. *J Am Acad Dermatol.* 2002;47:885-892.
15. Boyle F, Pendlebury S, Bell D. Further insights into the natural history and management of primary cutaneous neuroendocrine (Merkel cell) carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;31:315-323.
16. Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. *Arch Otolaryngol Head Neck Surg.* 2001;127:149-154.
17. McAfee WJ, Morris CG, Mendenhall CM, et al. Merkel cell carcinoma: treatment and outcomes. *Cancer.* 2005;104:1761-1764.
18. Meeuwissen JA, Bourne RG, Kearsley JH. The importance of postoperative radiation therapy in the treatment of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;31:325-331.
19. Morrison WH, Peters LJ, Silva EG, et al. The essential role of radiation therapy in securing locoregional control of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys.* 1990;19:583-591.
20. Poulsen M, Rischin D, Walpole E, et al. 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.
21. Smith DE, Bielamowicz S, Kagan AR, et al. Cutaneous neuroendocrine (Merkel cell) carcinoma. a report of 35 cases. *Am J Clin Oncol.* 1995;18:199-203.
22. Yiengpruksawan A, Coit DG, Thaler HT, et al. Merkel cell carcinoma. prognosis and management. *Arch Surg.* 1991;126:1514-1519.
23. Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. *ANZ J Surg.* 2005;75:275-281.
24. Eng TY, Boersma MG, Fuller CD, et al. A comprehensive review of the treatment of Merkel cell carcinoma. *Am J Clin Oncol.* 2007;30:624-636.
25. Andea AA, Coit DG, Amin B, et al. Merkel cell carcinoma: histologic features and prognosis. *Cancer.* 2008;113:2549-2558.