Merkel Cell Carcinoma: A Case Report With Treatment Summary and Updates

Kathryn Boyse; Elizabeth H. Foley, MD; Valentina Bradley, MD; Dwight Scarborough, MD

GOAL

To understand Merkel cell carcinoma (MCC)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the risk factors associated with MCC.
2. Explain the histopathology of MCC.
3. Describe the treatment options for MCC.

CME Test on page 348.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: November 2004.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only that credit that he/she actually spent in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Ms. Boyse and Drs. Foley, Bradley, and Scarborough report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

Merkel cell carcinoma (MCC) is a rare primary cutaneous neoplasm known for its propensity to develop early regional and distant metastasis. Fewer than 400 cases occur annually in the United States. MCC ranks as the most deadly of cutaneous malignancies, with a fatality rate of approximately 25%. Because of its aggressive nature, MCC is often resistant to surgery, radiation, and chemotherapy regimens. Standardized treatment patterns have not been established, and difficulty arises finding appropriate treatment for the elderly, who comprise the majority of patients with MCC.

Cutis. 2004;74:350-356.

Accepted for publication September 30, 2004.

Ms. Boyse is a fourth-year medical student at Ohio State University, Columbus. Drs. Foley and Bradley were fellows at Affiliated Dermatology, Dublin, Ohio. Dr. Scarborough is Assistant Clinical Professor in the Department of Dermatology, Ohio State University Hospital, Columbus.

Reprints: Dwight Scarborough, MD, Affiliated Dermatology, 650 Shawan Falls Dr, Dublin, OH 43017 (e-mail: adohio@youthfullook.com).

Merkel cell carcinoma (MCC) is a neuroendocrine tumor that has been described as a primary neuroendocrine carcinoma of the skin or "cutaneous APUDoma." Alternatively,

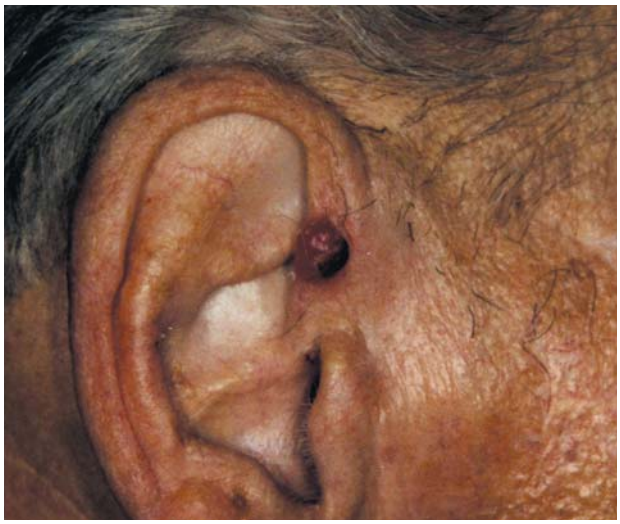

Figure 1. Initial presentation of Merkel cell carcinoma on the right ear.

MCC has been called a primary small cell carcinoma of the skin[1] because of its morphologic and behavioral similarities to small cell carcinoma of the lung.

Merkel cells are slowly adapting mechanoreceptors in epidermal nerve endings. Although they are found in ectoderm-derived skin and mucosa, recent evidence places their origin as neural crest.[2] Merkel cells contain cytokeratins and neuropeptide-containing eosinophilic granules. These cells combine with nerve terminals to form mechanoreceptors. It remains unclear if MCC originates from the same developmental lineage as Merkel cells. Recent research suggests these tumors originate from epidermal epithelial cells that are not in contact with nerve terminals but that have similar cytoskeletal filaments and a neuroendocrine origin.[2]

Although the pathogenesis of MCC has not been completely illuminated, it is agreed that UV exposure is an important risk factor. UVB-induced C • T transitions have been found, as well as p53 missense mutations. For this reason, risks include fair skin (as evidenced by the higher incidence in Caucasian populations), advanced age, and previous or concurrent sun-related skin malignancies such as squamous cell carcinoma and basal cell carcinoma.[3]

MCC also is linked to immunosuppression, with a higher incidence in transplant recipients and patients receiving chemotherapy.[4] In addition, there is an increased incidence in patients with psoriasis who were treated with psoralen-UVA. Reports link MCC to a history of prolonged arsenic exposure,[1] as well as to congenital dysplasia syndrome and chronic lymphocytic leukemia.[5]

MCC most often presents in fair-skinned patients 65 years and older as a solitary firm nodule on the head or neck. Its gross appearance is often nonspecific, being misdiagnosed as basal cell carcinoma or metastasis of a small cell carcinoma elsewhere.[2] Even when diagnosed at its earliest stage, MCC has a 2-year fatality rate of 10%. Its 5-year survival rate is 50% to 68%. Regional metastasis occurs in 50% to 60% of patients. When metastasis does occur, regional lymph nodes are involved 65% of the time,[6] with the majority (70%) occurring within 2 years of diagnosis. Nearly 40% will develop distant metastasis.[7] Metastases most commonly involve the skin, lymph nodes, liver, lung, and bone.[1] A primary lesion larger than 2 cm denotes a poor prognosis. There have been rare reports of spontaneous regression.

Histopathology

Microscopically, MCC can be difficult to identify. The epidermis may show bowenoid or squamous cell carcinoma–like changes, but they are not characteristic. Under low power microscopy, small round blue cells are evident in the dermis; the cells appear uniform and are often arranged to form either sheets or clusters that create a trabecular appearance or that of a group of grapes. On high power, the cells will appear to be pale and empty. Numerous mitoses can be identified, and evidence of metastasis can be found in the lymphatic or blood vessels. Neurosecretory granules that range from 80 to 120 nm and look like small blue dots[5] are membrane bound in the paranuclear regions.

Because traditional hematoxylin-eosin (H&E) staining demonstrates morphologic features of both epithelial and neuroendocrine tumors, H&E results cannot distinguish MCC from other small round blue cell tumors such as melanoma, lymphoma, neuroblastoma, and metastatic small cell lung carcinoma.[7] Cytokeratin staining and immunohistologic markers are required to make the definitive diagnosis; cytokeratin 20, chromogranin A, and synaptophysin are among those used. Other markers include neuron-specific enolase and, most recently, CD56, a marker for neural cell adhesion molecule.[8]

Case Report

In August 2002, an 86-year-old white man presented for evaluation of an 8-mm friable pink nodule on the right ear of uncertain duration (Figure 1). No cervical or peripheral adenopathy was appreciated. The man had an extensive history of prior basal cell carcinoma and squamous cell

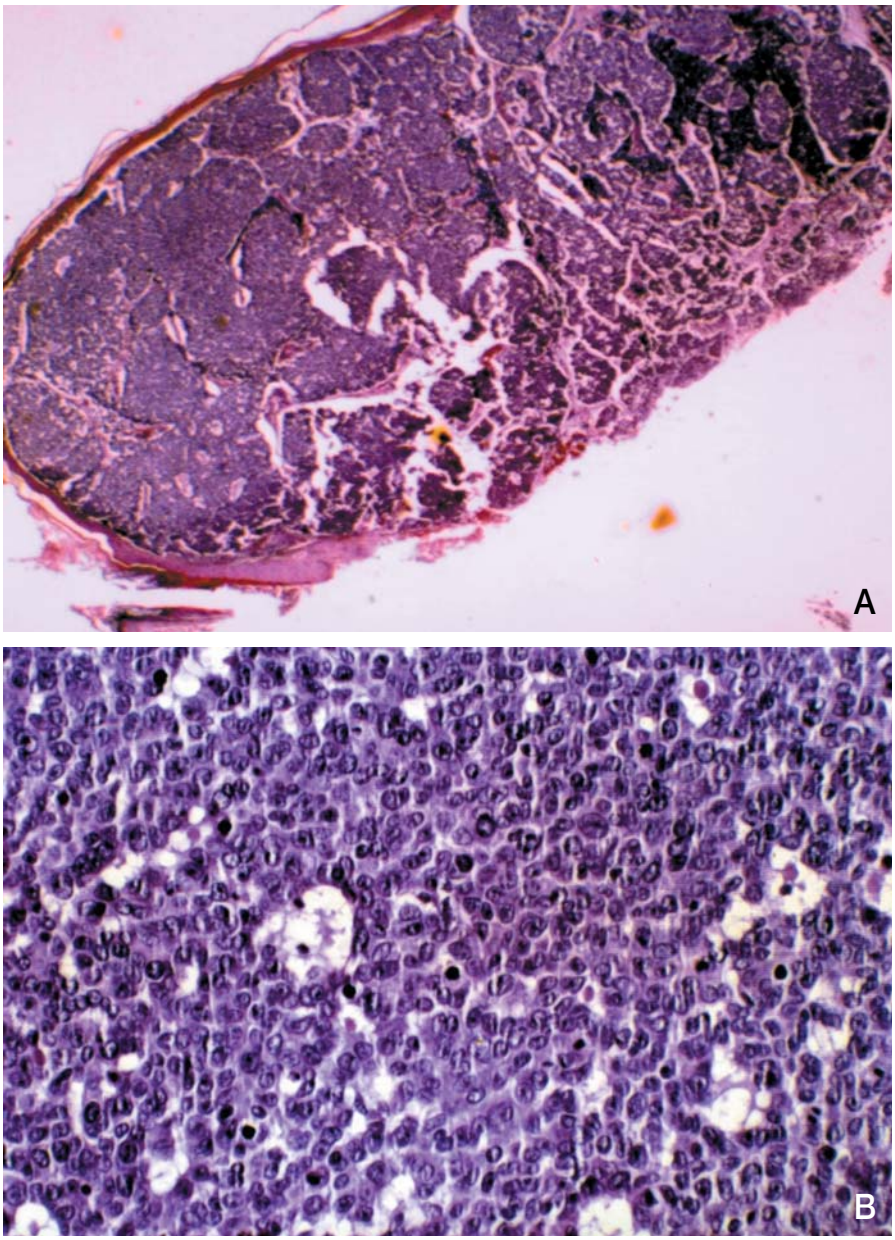

Figure 2. Aggregates of neoplastic cells with indistinct nucleoli with granular nucleoplasms and scant cytoplasms separated by fibrous septa or trabeculae (A and B)(H&E, original magnifications ×25 and ×250).

carcinoma on sun-exposed areas, having undergone excisions and Mohs micrographic surgery for many of these lesions.

An excisional biopsy was performed, and the pathology results revealed aggregates of neoplastic cells with indistinct nucleoli with granular nucleoplasms and scant cytoplasms separated by fibrous septa or trabeculae (Figure 2). Also, numerous mitotic figures and areas of focal necrosis were present. In our patient, cytokeratin 20 and chromogranin A results were strongly positive (Figures 3 and 4); although other entities can demonstrate either of these markers, when found together they confirm the diagnosis of MCC. Our patient also demonstrated CD56 positivity and a weakly positive reaction to synaptophysin (Figure 4). Cytokeratin 7 and CD45 results were negative, which also confirmed the diagnosis of MCC (Figure 5).

Staging by computed tomography scan of the neck, chest, and upper abdomen ruled out systemic spread. Because of the patient's advanced age, frail health status, and his adamant opposition, chemotherapy was deferred. Instead, he was referred to radiation oncology for a course of regional electron beam therapy. It was believed that radiation therapy might adequately control his

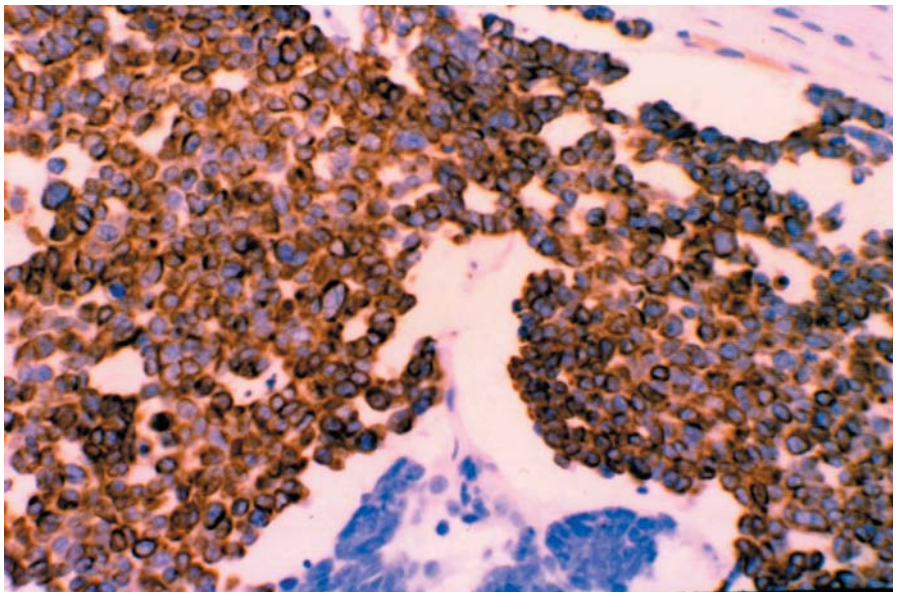

Figure 3. Positive reaction with cytokeratin 20 (original magnification ×250).

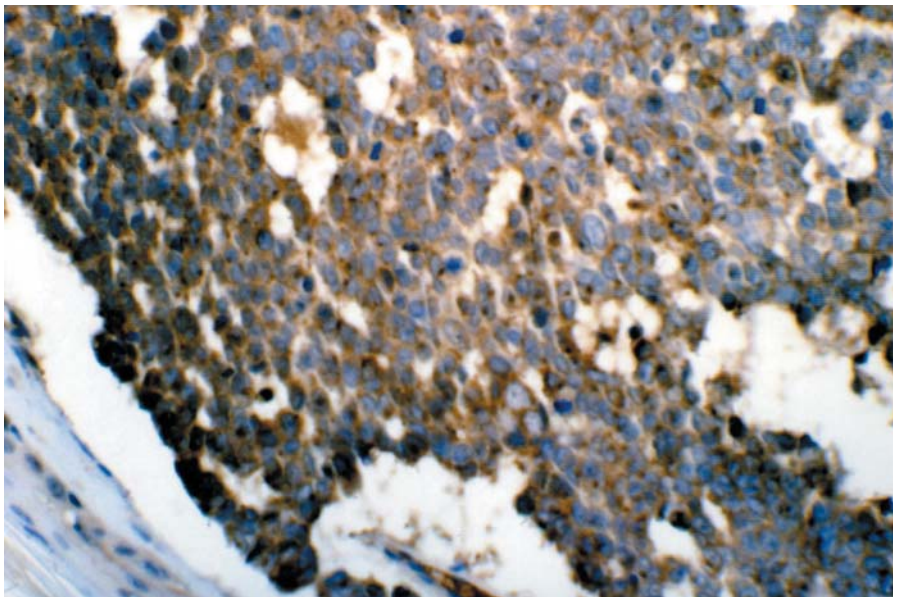

Figure 4. Positive reaction with chromogranin A (original magnification ×250).

disease and would not present the morbidity risks involved with chemotherapy and/or a more aggressive wide excision.[9] Six MeV radiation was used to deliver a 60-Gy surface dose to the ear area and 50 Gy to deep upper cervical nodes, facial nodes, and adjacent skin to the level of the larynx. The patient tolerated the 5 weeks of radiation treatment well, with mild skin erythema to the region.

The patient was followed closely; at a routine follow-up in February 2003, examination revealed a new 1-cm, right-sided preauricular pearly nodule. The patient revealed that the lesion had been present for 10 days. The new lesion appeared to be outside the previously treated radiation field. Excision was done using Mohs micrographic surgery, and the pathology results revealed clusters of undifferentiated neoplastic cells, some of which appeared to be within the lymphatics. This outcome, along with the immunohistochemistry results, confirmed that the lesion was the same histologic type as the primary lesion.

Shortly thereafter, the patient developed 2 new lesions on the right temple (0.8- and 1.3-cm irregular subcutaneous nodules). Pathology of these nodules also was consistent with MCC, with lymphatic and vascular involvement and positive margins of the

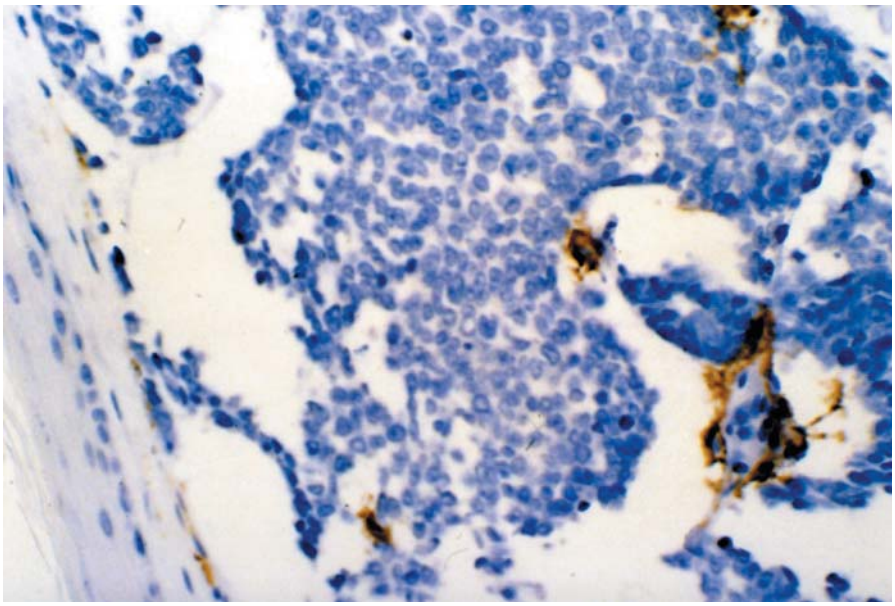

Figure 5. CD45 negative reaction (original magnification ×250).

resected area. The new lesions were then treated with a second course of electron beam therapy with a generous field that included some overlap with the previously irradiated area. Chemotherapy was again discussed with the patient, who strongly declined this option despite disease progression. His age and ability to tolerate the chemotherapeutic side effects involved were considerations in the patient's decision.

In October 2003, a second course of 6 MeV radiation to the right temple and anterior right cheek over 25 treatment sessions was completed. Despite the widened field of radiation, several new nodules developed during its course. These involved the superior aspect of the right ear, right nasolabial fold, upper left temple, left preauricular regions, and posterior neck.

In November 2003, a magnetic resonance image of the spine demonstrated systemic spread with bone metastasis involving the C2 and C3 vertebral bodies. A third round of radiation, now considered palliative, was directed to the cervical spine. With the patient finally concurring, a mild chemotherapeutic regimen of pamidronate and capecitabine also was planned. These treatments were discontinued after 2 courses because of failure to thrive. Bone metastases and cutaneous involvement continued to progress. Despite the unfavorable prognosis, the patient requested further treatment, and a single regimen of oral etoposide was chosen.

Comment

Treatment of a primary lesion without evidence of spread, or stage I disease, has historically been wide excision; however, acceptable margins have been debated, ranging from 1 to 3 cm. The addition of postsurgical irradiation of 50 to 60 Gy to the area of the lesion and all draining lymph node basins has been found to decrease local recurrence but has not been found to have a major impact on survival rates, given the frequency of distant metastasis in MCC.[10] Mortier et al[9] recently reported similar outcomes with radiation therapy alone and with wide excision followed by radiation for inoperable stage I disease. Prophylactic radiation (40–60 Gy) to the draining lymph node basin also has been proposed for stage I, though it has not been thoroughly investigated.

Mohs micrographic surgery may have a significant impact on the primary treatment of MCC. Local recurrence rates with Mohs micrographic surgery are lower than with wide excision because thorough histologic evaluation of margins is best.[11,12] Radiation at the primary site is indicated when clear margins cannot be achieved.[12] In the case of successful excision by Mohs micrographic surgery, adjuvant radiation therapy has not been shown to lower the rates of recurrence. However, irradiation of the lesion, including the draining lymph node basin, may improve regional control and increase the disease-free interval.[9]

MCC spreads to regional lymph nodes within 2 years in 70% of cases.[13] When lymph nodes are affected, 5-year survival is approximately 50%. Historically, regional lymphadenectomy was used in those patients with confirmed or suspected lymph node spread. Due to the morbidity risks of this

procedure, this technique has fallen out of favor.[14] A newer alternative is sentinel lymph node biopsy. The usefulness of this modality for the overall impact on survival is debated.[6]

Given the morphologic and immunohistologic similarities to small cell carcinoma, MCC also is similarly chemosensitive. Although there is no doubt about the efficacy of adjuvant chemotherapy in vitro, its benefit in preventing recurrence is debated. It is most widely accepted as a last-line effort in stage II disease to prevent progression to distant metastasis, and in stage III disease as a palliative effort.[15] In the limited studies of chemotherapy for cases of MCC, the response rate to first-line therapy approached only 65%. Dose-response figures have not been established.[11]

In the investigation into the use of chemotherapy as a first-line therapy, chemotherapy regimens employed in small cell lung carcinoma (cyclophosamide, doxorubicin, vincristine, or etoposide-cisplatin) may provide a useful guide. Although combinations such as cisplatin-doxorubicin are acceptable in patients younger than 65 years, elderly patients are often poor candidates given their comorbidities. Some monotherapy regimens, such as oral etoposide, have been successful.[10] Risks, including neutropenia and peripheral neuropathy, are magnified by the pharmacodynamic changes in absorption and metabolism that occur with age. Human growth factors such as granulocyte colony-stimulating factor, macrophage-macrophage colony-stimulating factor, and recombinant human erythropoietin have been supplemented in more elderly patients in an attempt to reduce morbidity and increase dose escalations.[11]

The lack of data on chemotherapy in the elderly population is not unique to MCC; rather, it is a common problem in cancer research. Most cancers occur in patients 65 years and older, yet there is a paucity of data on the effects of chemotherapy because elderly patients are poor candidates for phase 1 and phase 2 trials. Therefore, existing knowledge of the pharmacophysiology of aging must be used to extrapolate the most appropriate dosing and drug combinations.

New treatment modalities are being explored. Immunotherapy has shown some results for early stage MCC. Interferon alfa 2b and tumor necrosis factor have shown some promise. The antigens mucin 1 and epithelial cell adhesion molecule are expressed in 85% and 70% of MCC cases, respectively.[16] Current research is directed at developing antibodies to these antigens.

Somatostatin receptor scintigraphy along with sentinel lymph node biopsy might become another tool with which to detect micrometastasis. Reverse transcription polymerase chain reaction can be used to find markers such as cytokeratin 20 on MCC cells circulating in the peripheral blood pool.[17] This would allow identification of patients at high risk for systemic spread and relapse. To date, no treatment has been found to successfully arrest distant metastases.

Conclusion

Given the early dissemination of MCC and the poor prognosis once metastasis has occurred, aggressive treatment for stage I disease must be considered. Radiation therapy may be palliative and may have an increasing role as prophylactic protection in early disease. Chemotherapy has been employed in regional spread of disease (stage II). Will chemotherapy utilized in earlier stages of disease be a possible solution? Could combined chemoimmunotherapy be a useful compliment to the modest success of radiation treatment? These modalities are only as good as their practical use in the typical elderly patient with MCC, and addressing this challenge will be crucial in future research.

REFERENCES

1. Nghiem P, McKee PH, Haynes HA. Merkel cell (cutaneous neuroendocrine) carcinoma. In: Sober AJ, Haluska FG, eds. *Skin Cancer*. Hamilton, Ontario: BC Decker Inc; 2001;127-141.
2. Nathu RM, Mendenhall WM, Parsons JT. Merkel cell carcinoma of the skin. *Radiat Oncol Investig*. 1998;6:233-239.
3. Halata Z, Grim M, Bauman KI. Friedrich Sigmund Merkel and his "Merkel cell", morphology, development, and physiology: review and new results. *Anat Rec*. 2003;271A:225-239.
4. Kokoska E, Kokaska M, Collins B, et al. Early aggressive treatment for Merkel cell carcinoma improves outcome. *Am J Surg*. 1997;174:688-692.
5. Krasagakis K, Tosca AD. Overview of Merkel cell carcinoma and recent advances in research. *Int J Dermatol*. 2003;42:669-676.
6. Rodrigues L, Leong S, Kashani-Sabet M, et al. Early experience with sentinel lymph node mapping for Merkel cell carcinoma. *J Am Acad Dermatol*. 2001;45:303-308.
7. Hitchcock CL, Bland KI, Laney RG 3rd, et al. Neuroendocrine (Merkel cell) carcinoma of the skin. its natural history, diagnosis and treatment. *Ann Surg*. 1988;207:201-207.
8. Kurokawa M, Nabeshima K, Akiyama Y, et al. CD56: a useful marker for diagnosing Merkel cell carcinoma. *J Dermatol Sci*. 2003;31:219-224.
9. Mortier L, Mirabel X, Fournier C, et al. Radiotherapy alone for primary Merkel cell carcinoma. *Arch Dermatol*. 2003;139:1587-1590.

10. Fenig E, Brenner B, Katz A, et al. The role of radiation therapy and chemotherapy in the treatment of Merkel cell carcinoma. *Cancer*. 1997;80:881-885.
11. Voog E, Biron P, Martin J, et al. Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Am Cancer Soc*. 1999;85:2590-2595.
12. 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.
13. Mehrany K, Otley CC, Weenig RH, et al. A meta-analysis of the prognostic significance of sentinel lymph node status in Merkel cell carcinoma. *Dermatol Surg*. 2002;28:113-117.
14. Hill ADK, Brady MS, Coit DG. Intraoperative lymphatic mapping and sentinel lymph node biopsy for Merkel cell carcinoma. *Br J Surg*. 1999;86:518-521.
15. Brady MS. Current management of patients with Merkel cell carcinoma. *Dermatol Surg*. 2004;30:321-325.
16. Moll I, Kuhn C, Moll R. Cytokeratin 20 is a general marker of cutaneous Merkel cells while certain neuronal proteins are absent. *J Invest Dermatol*. 1995;104:900-915.
17. Durani BK, Klein A, Henze M, et al. Somatostatin analogue scintigraphy in Merkel cell tumours. *Br J Dermatol*. 2003;148:1135-1140.