Complete Remission of Metastatic Merkel Cell Carcinoma in a Patient With Severe Psoriasis

James Yousif, DO; Brandon Yousif, MS; Mark A. Kuriata, DO

PRACTICE **POINTS**

- Merkel cell carcinoma (MCC) has remarkable metastatic potential.
- Initial evaluation of patients with MCC should include clinical examination to detect cutaneous, lymph node, and distant metastasis.
- Risk factors associated with the development of MCC include immunosuppression, older age, and UV-exposed fair skin.

To the Editor:

A 69-year-old white man presented with a skin lesion on the back of 1 to 2 weeks' duration. The patient stated he was unaware of it, but his wife had recently noticed the new spot. He denied any bleeding, pain, pruritus, or other associated symptoms with the lesion. He also denied any prior treatment to the area. The patient's medical history was remarkable for severe psoriasis involving more than 80% body surface area, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, coronary artery disease, squamous cell carcinoma, and actinic keratoses. He had been on multiple treatment regimens over the last 20 years for control of psoriasis including topical corticosteroids, psoralen plus UVA and UVB phototherapy, gold injections, acitretin, prednisone, efalizumab, ustekinumab, and alefacept upon evaluation of this new skin lesion. Utilization of immunosuppressive agents also provided an additional benefit of controlling the patient's inflammatory arthritic disease.

On physical examination a 0.6×0.7-cm, pink to erythematous, pearly papule with superficial telangiectases was noted on the right side of the dorsal thorax (Figure 1). Multiple well-demarcated erythematous plaques with silvery scale and areas of secondary excoriation were noted on the trunk and both legs consistent with the patient's history of psoriasis.

A shave biopsy was performed on the skin lesion on the right side of the dorsal thorax with a suspected clinical diagnosis of basal cell carcinoma. Two weeks later the patient returned for a discussion of the pathology report, which revealed nodules of basaloid cells with tightly packed vesicular nuclei and scant cytoplasm in sheets within the superficial dermis, as well as areas of nuclear

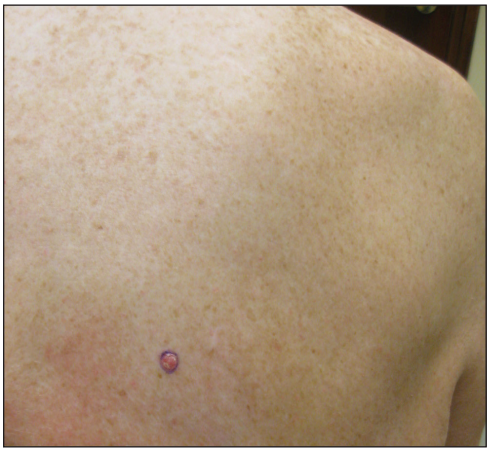

FIGURE 1. A 0.6×0.7-cm, pink to erythematous, pearly papule with superficial telangiectases on the right side of the dorsal thorax consistent with Merkel cell carcinoma.

Drs. Yousif and Kuriata are from the Department of Dermatology, Michigan State University College of Osteopathic Medicine/Lakeland Medical Center, St. Joseph, Michigan. Mr. Yousif is from the University of Michigan, Ann Arbor.

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Correspondence: James Yousif, DO, 3563 Walnut Brook Dr, Rochester Hills, MI 48309 (yousifja@msu.edu).

molding, numerous mitotic figures, and areas of focal necrosis (Figure 2). In addition, immunostaining was positive for cytokeratin (CK) 20 antibodies with a characteristic paranuclear dot uptake of the antibody. These findings were consistent with a diagnosis of Merkel cell carcinoma (MCC). At that time, alefacept was discontinued and he was referred to a tertiary referral center for further evaluation and treatment.

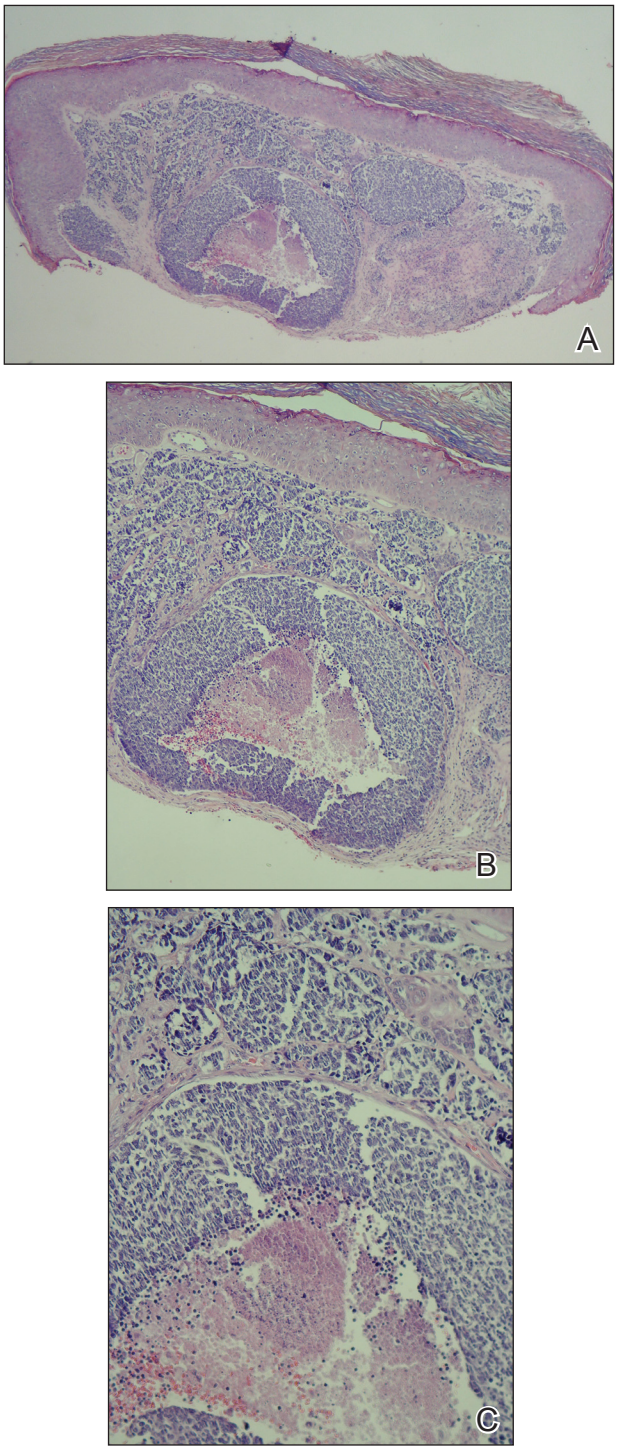

FIGURE 2. Histopathology demonstrated islands of blue basaloid cells within the dermis displaying numerous mitotic figures and areas of necrosis (A–C)(all H&E, original magnifications ×4, ×20, and ×40).

The patient subsequently underwent wide excision with 1-cm margins of the MCC, with intraoperative lymphatic mapping/sentinel lymph node biopsy (SLNB) of the right axillary nodal basin 1 month later, which he tolerated well without any associated complications. Further histopathologic examination revealed the deep, medial, and lateral surgical margins to be negative of residual neoplasm. However, one sentinel lymph node indicated positivity for micrometastatic MCC, consistent with stage IIIA disease progression.

He underwent a second procedure the following month for complete right axillary lymph node dissection. Histopathologic examination of the right axillary contents included 28 lymph nodes, which were negative for carcinoma. He continued to do well without any signs of clinical recurrence or distant metastasis at subsequent follow-up visits.

Approximately 2.5 years after the second procedure, the patient began to develop right upper quadrant abdominal pain of an unclear etiology. Computed tomography of the abdomen and pelvis was performed, revealing areas of calcification and findings consistent with malignant lymphadenopathy. Multiple hepatic lesions also were noted including a 9-cm lesion in the posterior right hepatic lobe. Computed tomography–guided biopsy of the liver lesion was performed and the findings were consistent with metastatic MCC, indicating progression to stage IV disease.

The patient was subsequently started on combination chemotherapeutic treatment with carboplatin and VP-16, with a planned treatment course of 4 to 6 cycles. He was able to complete a total of 6 cycles over a 4-month period, tolerating the treatment regimen fairly well. Follow-up positron emission tomography–computed tomography was within normal limits with no evidence of any hypermetabolic activity noted, indicating a complete radiographic remission of MCC. He was seen approximately 1 month after completion of treatment for clinical follow-up and monthly thereafter.

While on chemotherapy, the patient experienced a notable improvement in the psoriasis and psoriatic joint disease. Upon completion of chemotherapy, he was restarted on the same treatment plan that was utilized prior to surgery including topical corticosteroids, calcitriol, intramuscular steroid injections, and UVB phototherapy, which provided substantial control of psoriasis and arthritic joint disease. The patient later died, likely due to his multiple comorbidities.

Merkel cells are slow-responding mechanoreceptors located within the basal layer of the epidermis and are the source of a rare aggressive cutaneous malignancy.[1] Merkel cell carcinoma was first noted in 1972 and termed *trabecular carcinoma of the skin*, and it accounts for less than 1% of all nonmelanoma skin cancer.[2,3] This primary

neuroendocrine carcinoma has remarkable metastatic potential (34%–75%) and can invade regional lymph nodes, as well as distant metastasis most commonly to the liver, lungs, bones, and brain.[2] Approximately 25% of patients present with palpable lymphadenopathy and 5% with distant metastasis at the time of diagnosis. This frequency of metastasis at diagnosis as well as the recurrence after treatment contributes to the poor prognosis of MCC. Local recurrence rates have been reported at 25% with lymph node involvement in 52% and metastasis in 34%, with most recurrences occurring within 2 years of diagnosis. Patient mortality is dependent on the aggressiveness of the tumor, with 5-year survival rates of 83.3% without lymph node involvement, 58.3% with lymph node involvement, and 31.3% in those with metastatic disease.[4]

The tumor classically presents as a red to violaceous, painless nodule with a smooth shiny surface most often on the head and neck region.[4-6] Approximately 50% of MCC cases present in the head and neck region, 32% to 38% on the extremities, and 12% to 14% on the trunk.[1] This nonspecific presentation may lead to diagnostic uncertainty and a consequent delay in treatment. Definitive diagnosis of MCC is achieved with a skin biopsy and allows for distinction from other clinically similar–appearing neoplasms. Merkel cell carcinoma presents histologically as small round basophilic cells penetrating through the dermis in 3 histologic patterns: the trabecular, intermediate (80% of cases), and small cell type.[5] It may be differentiated immunohistochemically from other neoplasms, as it displays CK20 positivity (showing paranuclear dotlike depositions in the cytoplasm or cell membrane) and is negative for CK7. Chromagranin and synaptophysin positivity also may provide further histologic confirmation. In addition, absence of peripheral palisading, retraction artifact, and a fibromyxoid stroma allow for distinction from cutaneous basal cell carcinoma, which may display these features histologically. Other immunohistochemical markers that may be of value include thyroid transcription factor 1, which is typically positive in cutaneous metastasis of neuroendocrine carcinoma of the lung; S-100 and human melanoma black 45, which are positive in melanoma; and leukocyte common antigen (CD45), which can be positive in lymphoma. These stains are classically negative in MCC.[3]

Merkel cell carcinoma is commonly associated with the presence of Merkel cell polyomavirus (MCPyV) in tumor specimens, with a prevalence of 70% to 80% in all cases. Merkel cell polyomavirus is a class 2A carcinogen (ie, a probable carcinogen to humans) and is classified among a group of viruses that encode T antigens (ie, an antigen coded by a viral genome associated with transformation of infected cells by tumor viruses), which can lead to initiation of tumorigenesis through interference with cellular tumor suppressing proteins such as p53.[5] In addition, several risk factors have been associated with the development of MCC including immunosuppression, older age (>50 years), and UV-exposed fair skin.[7] One explanation for this phenomenon is the increase in MCPyV small T antigen transcripts induced by UV irradiation.[5] In addition, as with other cancers induced by viruses, host immunity can impede tumor progression and development. Therefore, impairment of normal immune function likely creates a higher risk for MCC development and potential for a worse prognosis.[3] Although the exact incidence of MCC in immunosuppressed patients appears unclear, chronic immunosuppressive therapy may play a notable role in the pathogenesis of the tumor.[3]

Although each of these factors was observed in our patient, it also was possible that his associated comorbidities further contributed to disease presentation. In particular, rheumatoid arthritis has been shown to carry an increased risk for the development of MCC.[8] In addition, inflammatory monocytes infected with MCPyV, as evidenced in a patient with a history of chronic psoriasis prior to diagnosis of MCC, also may contribute to the pathogenesis of MCC by traveling to inflammatory skin lesions, such as those seen in psoriasis, releasing MCPyV locally and infecting Merkel cells.[9] Although MCPyV testing was never performed in our patient, it certainly would be prudent as well as further studies determining the correlation of MCC to these disease processes.

Although regression is rare, multiple cases have documented spontaneous regression of MCC after biopsy of these lesions.[4,6,10] The exact mechanism is unclear, but apoptosis induced by T-cell immunity is suspected to play a role. Programmed cell death 1 protein (PD-1)–positive cells play a role. The PD-1 receptor is an inhibitory receptor expressed by T cells and in approximately half of tumor-infiltrating cells in MCC. It was found that in a regressed case of MCC there was a notably lower percentage of PD-1 positivity compared to cases with no apparent regression, suggesting that PD-1–positive cells suppress tumor immunity to MCC and that significant reduction in these cells may induce clinical regression.[10] Additional investigation would be beneficial to examine the relationship of this phenomenon to tumor regression.

Initial evaluation of these patients should include a meticulous clinical examination with an emphasis on detection of cutaneous, lymph node, and distant metastasis. Due to the risk of metastatic potential, regional lymph node ultrasonography and computed tomography of the chest, abdomen, and pelvis typically are recommended at baseline. Other imaging modalities may be warranted based on clinical findings.[3] Treatment modalities include various approaches, with surgical excision of the primary tumor with more than 1-cm margin to the fascial plane being the primary modality for uncomplicated cases.[1,3,7] In addition, SLNB also should be performed at the time of the procedure. In the case of a positive SLNB or suspected regional lymph node involvement upon initial examination, radical regional lymph node dissection also is recommended.[3] Although some authorities advocate postsurgical radiation therapy to minimize the risk of local

recurrence, there does not appear to be a clear benefit in survival rate.[3,5] However, radiation treatment as monotherapy has been advocated in certain instances, particularly in cases of unresectable tumors or patients who are poor surgical candidates.[5,7] Cases of distant metastasis (stage IV disease) may include management with surgery, radiation, and/or chemotherapy. Although none of these modalities have consistently shown to improve survival, there appears to be up to a 60% response with chemotherapy in these patients.[3]

Because MCC tends to affect an older population, often with other notable comorbidities, important considerations involving a treatment plan include the cost, side effects, and convenience for patients. The combination of carboplatin and VP-16 (etoposide) was utilized and tolerated well in our patient, and it has been successful in achieving complete radiologic and clinical remission of his metastatic disease. This combination appears to prolong survival in patients with distant metastasis, as compared to those patients not receiving chemotherapy.[1] Our patient has since died, but in these high-risk patients, close clinical monitoring is essential to help optimize their prognosis.

Merkel cell carcinoma is a rare aggressive cutaneous neoplasm that most commonly affects the elderly, immunosuppressed, and those with chronic UV sun damage. An association between the oncogenesis of MCC and infection with MCPyV has been documented, but other underlying diseases also may play a role in this process including rheumatoid arthritis and psoriasis. Although these risk factors were associated with our patient, his history of chronic immunosuppressive therapy for treatment of his psoriasis and inflammatory joint disease likely played a role in the pathogenesis of the tumor and should be an important point of discussion with any patient requiring this type of long-term management for disease control. Our unique clinical case highlights a patient with substantial comorbidities who developed metastatic MCC and achieved complete clinical and radiologic remission after treatment with surgery and chemotherapy.

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