Spontaneous Regression of Merkel Cell Carcinoma

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PRACTICE **POINTS**

- Merkel cell carcinoma (MCC) is a rare malignancy with a high rate of metastasis and poor prognosis.
- T-cell mediated immunity appears to play an important role in tumor regression in MCC.
- Merkel cell polyomavirus appears to play a role in the pathogenesis of MCC and may be associated with a better prognosis.
- A better understanding of spontaneous regression of MCC could help in the development of new immunotherapeutic approaches to this malignancy.

A 96-year-old woman presented with a rapidly enlarging lesion overlying the suprasternal notch. The lesion originated as a small, erythematous, scaly macule that rapidly increased in size over 8 weeks and became an ulcerated nodule measuring 5 cm in diameter and 4.5 cm in thickness. A 4-mm punch biopsy showed a poorly differentiated tumor with cells that were positive for CAM 5.2 and cytokeratin 20 in a dotlike paranuclear pattern and negative for cytokeratin 5/6, human melanoma black 45, and leukocyte common antigen. Two weeks after the punch biopsy, the lesion noticeably decreased in size, and within 8 weeks of the biopsy the tumor had completely resolved with no further intervention. Regression of Merkel cell carcinoma (MCC) is a very rare event, with as few as 30 cases reported. The mechanism of this phenomenon remains unclear; however, T-cell–mediated immunity and apoptosis appear to play a major role.

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Merkel cell carcinoma (MCC) is a rare, rapidly growing, aggressive neoplasm with a generally poor prognosis. The cells of origin are highly anaplastic and share structural and immunohistochemical features with various neuroectodermally derived cells. Although Merkel cells, which are slow-acting cutaneous mechanoreceptors located in the basal layer of the epidermis, and MCC share immunohistochemical and ultrastructural features, there is limited evidence of a direct histogenetic relationship between the two.[1,2] Additionally, some extracutaneous neuroendocrine tumors have features similar to MCC; therefore, although it may be more accurate and perhaps more practical to describe these lesions as primary neuroendocrine carcinomas of the skin, the term *MCC* is more commonly used both in the literature and in clinical practice.[1,2]

Merkel cell carcinoma typically presents in the head and neck region in white patients older than 70 years of age and in the immunocompromised population.[3-6] The mean age of diagnosis is 76 years for women and 74 years for men.[7] The incidence of MCC in the United States tripled over a 15-year period, and there are approximately 1500 new cases of MCC diagnosed each year, making it about 40 times less common than melanoma.[8] The 5-year survival rate for patients without lymph node involvement is 75%, whereas the 5-year survival rate for patients with distant metastases is 25%.[9]

Merkel cell carcinoma is thought to develop through 1 of 2 distinct pathways. In a virally mediated pathway, which represents at least 80% of cases, the Merkel cell polyomavirus (MCV) monoclonally integrates into the

AUDIO **ONLINE**

Dr. Sean Branch discusses spontaneous regression of MCC with *Cutis* Editor-in-chief Vincent A. DeLeo, MD, in a "Peer to Peer" audiocast

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host genome and promotes oncogenesis via altered p53 and retinoblastoma protein expression.[10-12] The remainder of cases are believed to develop via a nonvirally mediated pathway in which genetic anomalies, immune status, and environmental factors influence oncogenesis.[10-13]

Due to the similarity between MCC and metastatic neuroendocrine neoplasms, especially small-cell lung carcinomas, immunohistochemistry is important in making the diagnosis. Cytokeratin 20 and neuron-specific enolase positivity and thyroid transcription factor 1 negativity are the most useful markers in identifying MCC.

Regression of MCC is a very rare and poorly understood event. A 2010 review of the literature described 22 cases of spontaneous regression.[14] We report a rare case of rapid and complete regression of MCC following punch biopsy in a 96-year-old woman.

Case Report

A 96-year-old woman presented with a rapidly enlarging lesion overlying the suprasternal notch of 8 weeks' duration (Figure 1). The lesion consisted of a 5.0×4.5-cm, friable, erythematous, flesh-colored nodule with ulceration and heavy crusting. Surrounding the nodule was an erythematous to violaceous patch extending to the anterior chest and bilateral supraclavicular area. No cervical or clavicular lymphadenopathy was observed. According to the patient's caregiver, the lesion originated as a small, erythematous, scaly macule that rapidly increased in size over an 8-week period to a maximum of 5.0×4.5 cm at presentation. The lesion bled on 2 or 3 occasions during the 8-week period and was controlled with a warm compress. The patient's caregiver had treated the lesion with topical tea tree oil (for malodor) and antibiotic ointment as needed. The clinical differential diagnosis included squamous cell carcinoma, keratoacanthoma, amelanotic melanoma, cutaneous metastasis of a primary visceral malignancy, basal cell carcinoma, and MCC. Biopsy of the lesion was recommended at this time but the patient's family declined.

A 4-mm punch biopsy was obtained at a follow-up visit 4 weeks later (12 weeks after the reported onset of the lesion). Hematoxylin and eosin staining showed a small-cell neoplasm with stippled nuclei and scant cytoplasm forming a nested and somewhat trabecular pattern. Mitotic activity, apoptosis, and nuclear molding also were present (Figure 2). The tumor cells were positive for cytokeratin 20 with a dotlike, paranuclear pattern (Figure 3). Staining for CAM 5.2 also was positive. Cytokeratin 5/6, human melanoma black 45, and leukocyte common antigen were negative. The immunophenotyping of the lymphocytic response to the tumor showed that the majority of intratumoral lymphocytes were CD8 positive (Figure 4). CD4-positive lymphocytes were predominantly seen at the periphery of the tumor nests without tumor infiltration (Figure 5). Based on these findings, a diagnosis of MCC was made. The patient's family declined treatment based on her

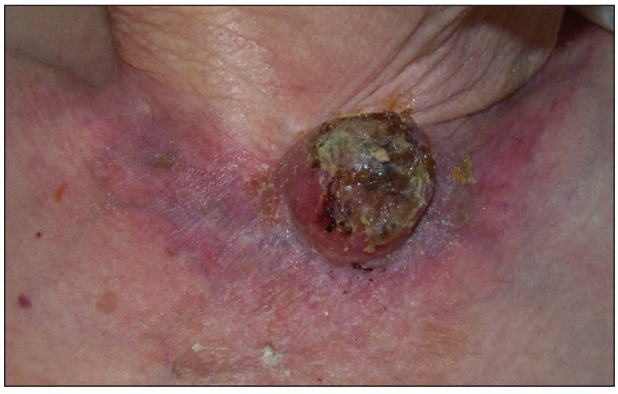

FIGURE 1. Merkel cell carcinoma presenting as a 5.0×4.5-cm friable, erythematous, flesh-colored nodule with ulceration and a thick crust overlying the suprasternal notch in a 96-year-old woman 8 weeks after onset.

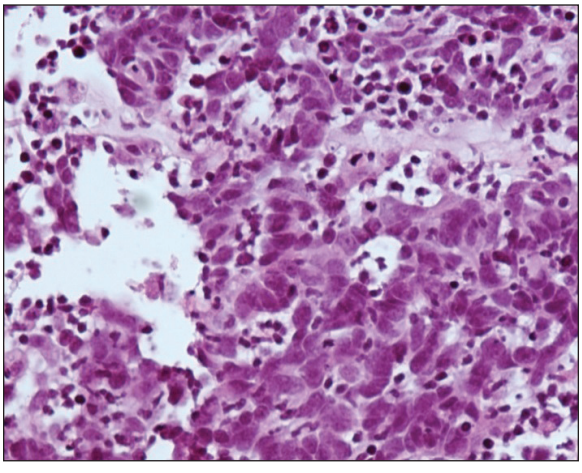

FIGURE 2. Small-cell neoplasm with stippled nuclei and scant cytoplasm forming a nested and somewhat trabecular pattern. Mitotic activity, apoptosis, and nuclear molding also were observed (H&E, original magnification ×20).

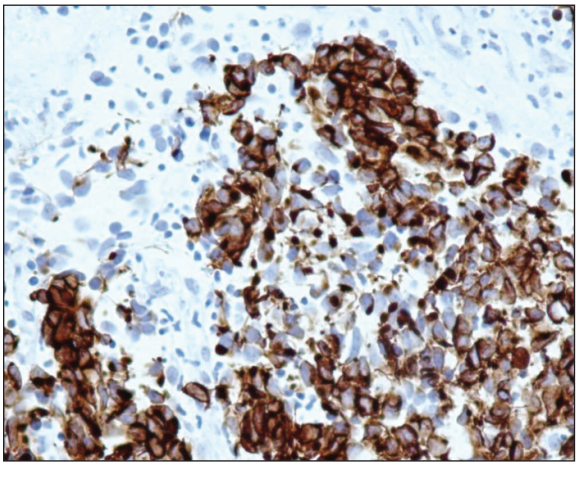

FIGURE 3. Merkel cell carcinoma tumor cells stained positive for cytokeratin 20 in a dotlike paranuclear pattern (original magnification ×20).

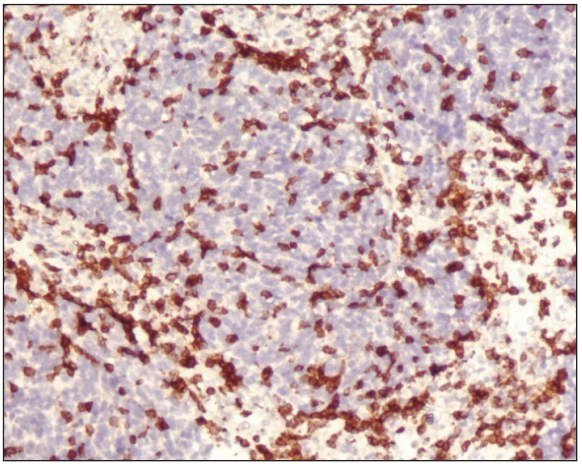

FIGURE 4. CD8-positive lymphocytes infiltrating tumor nests in a patient with Merkel cell carcinoma (original magnification ×10).

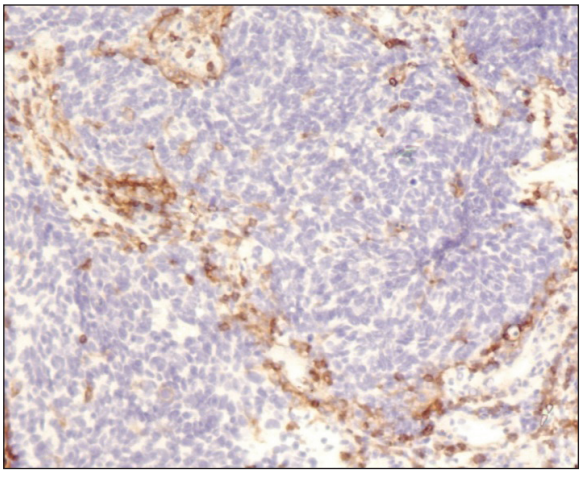

FIGURE 5. CD4-positive lymphocytes presenting predominantly at the periphery of tumor nests in a patient with Merkel cell carcinoma (original magnification ×10).

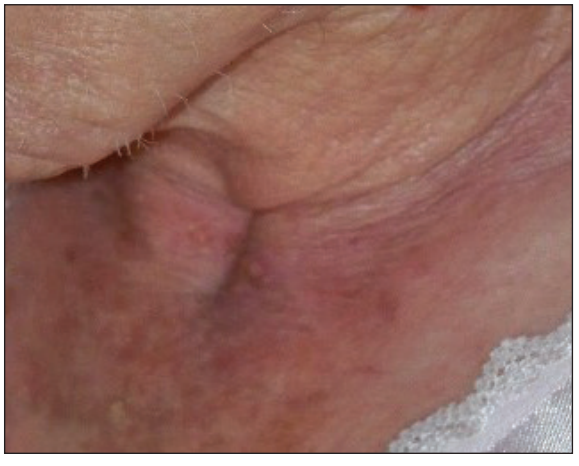

FIGURE 6. Complete resolution was observed at 20 weeks' follow-up after spontaneous regression of the Merkel cell carcinoma.

advanced age and current health status, which included advanced dementia.

Two weeks after the punch biopsy, the lesion had noticeably decreased in size and lost its dome-shaped appearance. Within 8 weeks after biopsy (20 weeks since the lesion first appeared), the lesion had completely resolved (Figure 6). The patient was lost to follow-up months later, but no recurrence of the lesion was reported.

Comment

Spontaneous regression is not unique to MCC, as this phenomenon also has been reported in keratoacanthoma, lymphoma, basal cell carcinoma, and melanoma.[15] Complete spontaneous regression is defined as occurring in the absence of therapy that is intended to have a treatment effect.[15,16] Spontaneous regression is estimated to occur in malignant neoplasms at a rate of 1 case per 60,000 to 100,000 (approximately 0.0013% of all malignant neoplasms).[17] Considering the reported prevalence of MCC and the number of cases that have been known to regress, the estimated incidence of complete spontaneous regression may be as high as 1.5%.[14] Though spontaneous regression of MCC is more prevalent than expected, it still is considered a rare phenomenon. A 2010 review of the literature yielded 22 cases of complete spontaneous regression of MCC.[14] No recurrences have been observed; however, follow-up was relatively short in some cases.

In a unique report by Bertolotti et al,[18] a patient with MCC on the nasal tip presented 4 weeks after biopsy with complete spontaneous regression of the tumor, which was associated with bilateral cervical lymph node involvement as noted by hypermetabolic uptake on positron emission tomography scanning. The patient underwent radiation therapy and was disease free at 12 months' follow-up.[18]

Complete spontaneous regression has been described in MCC patients with local disease, regional recurrences, and metastatic disease.[19] In all reviewed cases, the regression is a fairly quick phenomenon occurring over the course of 1 to 5 months.[16,19,20,21] Our patient presented with advanced age and a tumor location characteristic of MCC. In our search of PubMed articles indexed for MEDLINE using the terms *MCC*, *Merkel cell carcinoma*, *regression*, and *spontaneous regression*, all but 1 case of MCC regression involved tumors that were located on the head.[14]

The histopathologic features observed in our case, specifically intratumoral CD8-positive cytotoxic lymphocytes and peritumoral CD4-positive cells, were similar to the findings in other reported cases. In one series of 2 cases, the one case showed scar tissue with a moderate, predominantly T-lymphocytic infiltrate and no tumor cells, and the second showed cellular proliferation in the deep dermis with dense lymphocytic infiltrates primarily composed of CD3-positive T cells.[14] Other studies of regression of both localized and metastatic MCC demonstrated infiltration by CD4-positive, CD8-positive, and CD3-positive lymphocytes and foamy macrophages.[21-23]

The discovery of the MCV was one of the most important advances in elucidating the pathogenesis of MCC.[10,24-26] Merkel cell polyomavirus DNA has been detected in a majority of MCC cases.[25,27] Viral integration has been shown to take place early, prior to tumor clonal expansion.[10] Importantly, not all cases of MCC show MCV infection, and MCV infection is not exclusive to MCC.[28] Merkel cell polyomavirus is considered to be part of the normal human flora, and asymptomatic infection is quite common.[29] It has been identified in 80% of adults older than 50 years of age and, interestingly, in 35% of children by 13 years of age or younger.[30,31] It remains unclear what role the presence of MCV plays in determining MCC prognosis. Several reports have demonstrated lower disease-specific mortality associated with MCV-positive MCC.[32-35] In contrast, Schrama et al[36] correlated the MCV status of 174 MCC tumors and found no difference in clinical behavior or prognosis between MCV-positive and MCV-negative MCCs.

Immunosuppression also may play a role in the development of MCC.[5,25] There is increased prevalence of MCC in the human immunodeficiency virus–positive population, as well as in organ-transplant recipients and patients with leukemia. Chronic lymphocytic leukemia seems to be the most frequent neoplasia associated with development of MCC.[37]

The mechanism of MCC regression remains unclear, but many investigators emphasize the importance of T-cell–mediated immunity.[16,21-23,38,39] Apoptosis also has been shown to play an important role.[40] Our case showed tumor-infiltrating CD8-positive lymphocytes and CD4-positive lymphocytes present predominantly at the periphery of the tumor, with close proximity to the tumor nests but with no tumor infiltration (Figure 3). This distribution was consistently present in multiple sections of the tumor. These findings are consistent with prior reports of both CD4-positive and CD8-positive T lymphocytes associated with MCC regression. Our findings confirm that immune response may play an important role in spontaneous regression of MCC.

There is much speculation regarding the initial biopsy of an MCC lesion (or other traumatic event) and its role in tumor regression. Koba et al[41] examined the effect of biopsy on CD8-positive lymphocytic infiltration of MCC tumor cells and found that biopsy does not commonly alter intratumoral CD8-positive infiltration. These findings suggest trauma does not directly induce immunologic recognition of this cancer.

Conclusion

We report a case of complete spontaneous regression of a localized MCC following a punch biopsy. The histopathology showed a brisk T-lymphocyte response with intratumoral CD8-positive cytotoxic lymphocytes and peritumoral CD4-positive cells. The age and clinical profile of our patient as well as the clinicopathologic characteristics of the tumor regression are similar to other reported cases. Further research is needed to elucidate the mechanism of MCC regression, and a better understanding of this fascinating phenomenon could help in development of new immunotherapeutic approaches.

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