FEATURE ARTICLE

NC PD 2.0 Contact Hours

Skin Cancer: Back to Basics—Merkel Cell Carcinoma

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ABSTRACT: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. Advanced disease portends a poor prognosis in most patients. We review the pathogenesis, clinical features, dermoscopic findings, differential diagnosis, workup, treatment modalities, and follow-up of MCC for dermatology nurses. It is important for nurses to be familiar with MCC to prevent delayed diagnosis.

Key words: Dermoscopy, Malignancy, Merkel, Merkel Cell Carcinoma, Skin Cancer

BACKGROUND

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor that is associated with a high rate of recurrence and distant metastases. It most commonly affects elderly white men over the age of 70 years with an extensive history of past sun exposure, although MCC has been reported in Black, Asian, American Indian, and Pacific Islander populations. The risk of MCC is up to 25 times higher in the white population, compared with other ethnicities (Coggshall et al., 2018; Goldstein & DeCaprio, 2019). MCC typically occurs on the sun-exposed areas of the head and neck (Coggshall et al., 2018). The incidence of MCC has increased steadily over the past 30 years and continues to increase; however, it remains low, with approximately 1,600 cases diagnosed annually in the United States (Coggshall et al., 2018; Tello et al., 2018). Annual incidence is much higher in patients with lymphoproliferative malignancies, history of solid organ transplant, and HIV infection (Goldstein & DeCaprio, 2019; Ma & Brewer, 2014). MCC is highly aggressive, and more than one third of patients die of the disease; thus, MCC has a case fatality rate that is currently higher than melanoma (Becker et al., 2017). Despite its rarity, it is important for dermatology nurses to be familiar with MCC because of its high case fatality rate.

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PATHOGENESIS

The current understanding of MCC is that it is a primary cutaneous tumor derived from the Merkel cell (MC). MCs are considered neuroendocrine cells that play a role in light touch/sensory responses and nerve guidance, as well as endocrine/paracrine effects and somatostatin synthesis (Coggshall et al., 2018). Oncogenesis of the MC is considered secondary to genetic and environmental factors. Evidence supports a role of ultraviolet (UV) radiation, with increased incidence on sun-exposed sites. In fact, patients with psoriasis treated with psoralen and UVA light were found to have a 100-fold increase in MCC development (Lunder & Stern, 1998). Immunosuppression and immunosenescence also play a role, with higher rates seen in patients on immunosuppressive therapies (10-fold increased risk in transplant patients), in those with HIV/AIDS (13-fold increased risk), and among the elderly population (with 76% of cases in people older than 65 years; Agelli & Clegg, 2003; Arora et al., 2012).

In 2008, Feng et al. discovered the MC polyomavirus (MCV) and found MCV's DNA to be integrated into the host cell's genome in a clonal pattern. MCV was found in eight of 10 (80%) MCC tumors, versus only five of 59 (8%) control tissues from various body sites and four of 24 (16%) control skin tissues (Feng et al., 2008). Since then, this has been further corroborated with 1,743 of 2,354 (74.2%) MCC tumors testing positive for MCV in multiple studies worldwide (Arora et al., 2012). Interestingly, although MCV is ubiquitous in humans (~60%–80% positive serologic tests in the general population), integration into the host genome is not part of the normal life cycle of MCV and integration inhibits the virus's ability to replicate. It has been postulated that UV radiation may induce mutations in MCV that drive integration into the genome and subsequent oncogenesis (Coggshall et al., 2018).

CLINICAL FEATURES

MCC most commonly presents as a rapidly growing cutaneous pink/red-to-violaceous nodule on the sun-exposed areas of the head, neck, or extremities of an elderly white man (Becker et al., 2017; Coggshall et al., 2018). The mnemonic AEIOU summarizes the clinical features that may raise suspicion for MCC (Figures 1 and 2; Heath et al., 2008). In one cohort study of 195 patients diagnosed with MCC, 89% of primary MCCs had three or more of these features (Heath et al., 2008). MCC has also been described in the literature to present with a plaque-like appearance surrounded by small satellite lesions, as a pink plaque, a cyst-like structure, a pruritic tumor on the lower extremities, a pedunculated papule, a subcutaneous mass, or a telangiectatic papule (Coggshall et al., 2018; Ramahi et al., 2013). Mucosal MCC is a rare entity and is more aggressive than cutaneous MCC (Coggshall et al., 2018). Metastatic MCC with no known primary is rare and represents only 4% of all cases (Coggshall et al., 2018).

Mnemonic for features of MCC: AEIOU
Asymptomatic/lack of tenderness
Expanding rapidly
Immune suppression
Older than age 50
UV-exposed site on a person with fair skin

DERMOSCOPY

MCC is one of the most aggressive cutaneous malignancies, and diagnosis is often delayed, partially because of rarity and of its nonspecific clinical features. There are no specific dermatoscopic features of MCC. In one review of 10 tumors, all showed an irregular vascular pattern, milky-red globules, and numerous linear irregular vessels on dermoscopy; however, there was no histopathological correlation observed (Harting et al., 2012). The dermatoscopic features observed in MCC and amelanotic melanoma overlap; however, the presence of a polymorphic vascular pattern may cue the clinician toward suspecting MCC (Dalle et al., 2012). Regardless, MCC cannot be diagnosed by dermoscopy alone, and a skin biopsy is needed to confirm the diagnosis.

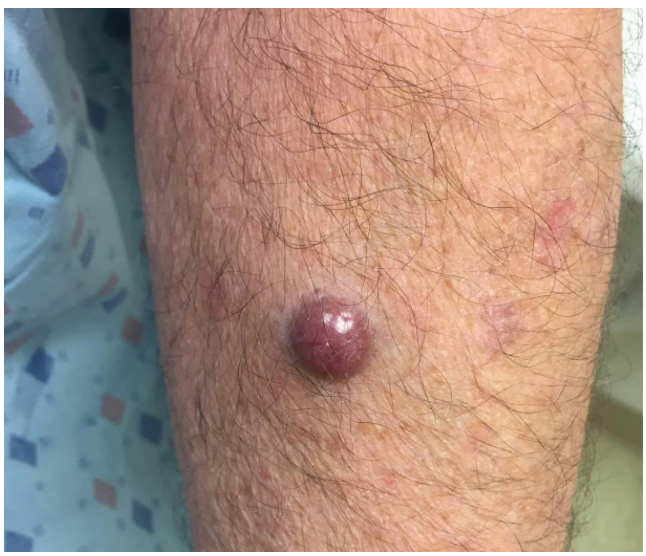

FIGURE 1. Merkel cell carcinoma presenting as a pink-to-violaceous nodule on the arm of an elderly white man.

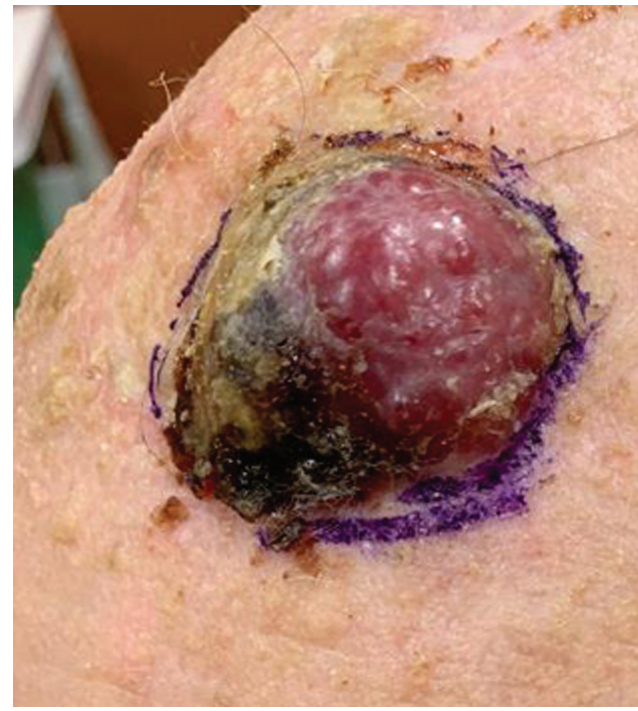

FIGURE 2. Merkel cell carcinoma presenting on the scalp of an elderly white man as a rapidly growing, friable pink nodule with a hemorrhagic crust.

HISTOPATHOLOGY OF MCC

On hematoxylin–eosin stains, MCC appears as a dermal tumor composed of sheets of basaloid cells with a granular "salt-and-pepper" chromatin pattern, scant cytoplasm, and scattered mitotic figures or apoptotic cells. The tumor stains positive for Cytokeratin 20 in a perinuclear dot pattern and also stains positive for synaptophysin, chromogranin, and neuron-specific enolase (Coggshall et al., 2018; Elston et al., 2019). An experienced dermatopathologist should interpret biopsy results, to ensure the appropriate immunostains that are needed to confirm the diagnosis of MCC are done.

DIFFERENTIAL DIAGNOSIS

The clinical differential diagnosis of MCC includes basal cell carcinoma, squamous cell carcinoma, leukemia cutis, inflamed epidermal inclusion cyst, lipoma, dermatofibroma, amelanotic melanoma, lymphoma, sarcoma, epidermal inclusion cyst, and metastatic carcinoma (Ramahi et al., 2013). Suspicion for MCC that presents as a subcutaneous, cyst-like nodule may be increased if a patient has pertinent risk factors (such as being an older adult, white, and immunosuppressed) and if a punctum is

not visible clinically. Suspicion for MCC may be heightened by a history of a lesion that is expanding rapidly (doubling in less than 3 months), chronic immunosuppression, age older than 50 years, and lesion location on a UV-exposed area (Sarnaik et al., 2010).

WORKUP AND TREATMENT MODALITIES

The National Comprehensive Cancer Network (NCCN) in the United States proposed specific, updated guidelines for diagnostic evaluation of MCC; these guidelines review the clinical presentation, preliminary workup, diagnosis, additional workup, and then treatment depending on staging (NCCN, 2019). A table outlining a simplified version of the 2019 NCCN guideline is shown below (Table 1).

If a lesion suspicious for MCC is identified on examination, a skin biopsy should be performed and sent for hematoxylin-and-eosin and immunopanel studies, and the patient should have a complete skin and lymph node examination. The provider should note suspicion for MCC on the pathology requisition for the biopsy to aid the dermatopathologist in making an accurate diagnosis. Upon diagnosis of MCC, the patient should be referred to an oncologist for appropriate staging and further workup according to NCCN (2019) guidelines.

For patients with clinically negative lymph nodes, the most reliable tool for evaluating regional nodes for metastases is a sentinel lymph node biopsy (SLNB; Coggshall et al., 2018). SLNB is recommended in patients with clinically negative lymph nodes because approximately 26% of these patients will have pathologically positive lymph nodes (Allen et al., 2005; Lemos & Ngheim, 2007; Sims et al., 2018). Every effort should be made for SLNB to be performed preceding or concurrently with excision to prevent a false-negative SLNB result (NCCN, 2019). Imaging at the time of diagnosis using magnetic resonance imaging, computed tomography, or positron emission tomography/computed tomography may be ordered as clinically indicated (Coggshall et al., 2018). Excision of the tumor by a board-certified dermatologist or surgical oncologist is the first-line therapy; however, if not feasible, radiation monotherapy may be considered (NCCN, 2019). For advanced-stage or refractory MCC, chemotherapy or immune-checkpoint inhibitors may be utilized by oncology (Becker et al., 2017; NCCN, 2019).

TABLE 1. Summary of National Cancer Coalition Network: Merkel Cell Carcinoma 2019 Guidelines

1. Complete skin and lymph node examination
2. Biopsy specimen, sent to an experienced dermatopathologist for hematoxylin–eosin stains and immunostaining
3. For patients with negative clinical nodes, refer to oncology to obtain a sentinel lymph node biopsy
4. For patients with positive clinical nodes, refer to oncology for fine needle aspiration or core biopsy first
   a. If negative, oncology may consider open lymph node biopsy
   b. If positive, oncology may proceed to 5
5. Imaging as clinically indicated with magnetic resonance imaging, computed tomography (CT), or positron emission tomography/CT
6. Consider consultation with a multidisciplinary tumor board

ROLE OF THE DERMATOLOGY NURSE

Because of the rarity and aggressiveness of MCC, it is important for nurses (such as licensed practical nurses, registered nurses, and nurse practitioners) to be familiar with its clinical features and management to ensure timely diagnosis and appropriate course of care. Patients face much uncertainty amid a diagnosis of MCC. Nurse practitioners may conduct skin cancer screenings and perform skin biopsies, so familiarity with MCC is critical to prevent delayed diagnosis. Nurse practitioners who diagnose MCC need to also be aware of appropriate treatment and follow-up so that timely and appropriate referral can be made to oncology. Nurses at all levels of practice also may play an important role in educating patients about risk factors and clinical features of MCC. Any nurse caring for a patient with MCC may be expected to provide patient education and help guide the patient through treatment and follow-up. A team-based approach to treatment with coordination of care between dermatology, surgery, and oncology is necessary, and nurses may help to facilitate care coordination. Knowledge of MCC enables nurses to provide the best possible care to patients with MCC, within the nurses' scope of practice and specialty.

FOLLOW-UP

MCC is an aggressive tumor with a poor prognosis, especially if there is metastatic disease at presentation. At 5 years, overall survival is approximately 51% for local disease, 35% for nodal disease, and 14% for distant metastatic disease (Harms et al., 2016). Patients with a history of MCC should undergo a complete skin and lymph node examination every 3–6 months for 3 years and then every 6–12 months indefinitely (NCCN, 2019). For high-risk patients, routine imaging may be considered to monitor for metastasis. ■

REFERENCES

Agelli, M., & Clegg, L. X. (2003). Epidemiology of primary Merkel cell carcinoma in the United States. *Journal of the American Academy of Dermatology*, *49*(5), 832–841. 10.1016/s0190-9622(03)02108-x

Allen, P. J., Bowne, W. B., Jaques, D. P., Brennan, M. F., Busam, K., & Coit, D. G. (2005). Merkel cell carcinoma: Prognosis and treatment of patients from a single institution. *Journal of Clinical Oncology*, *23*(10), 2300–2309.

Arora, R., Chang, Y., & Moore, P. S. (2012). MCV and Merkel cell carcinoma: A molecular success story. *Current Opinion in Virology*, *2*(4), 489–498. 10.1016/j.coviro.2012.05.007

Becker, J. C., Stang, A., DeCaprio, J. A., Cerroni, L., Lebbé, C., Veness, M., & Nghiem, P. (2017). Merkel cell carcinoma. *Nature Reviews Disease Primers*, *3*, 17077. 10.1038/nrdp.2017.77

Coggshall, K., Tello, T. L., North, J. P., & Yu, S. S. (2018). Merkel cell carcinoma: An update and review: Pathogenesis, diagnosis, and staging. *Journal of the American Academy of Dermatology*, *78*(3), 433–442. 10.1016/j.jaad.2017.12.001

Dalle, S., Parmentier, L., Moscarella, E., Phan, A., Argenziano, G., & Thomas, L. (2012). Dermoscopy of Merkel cell carcinoma. *Dermatology (Basel, Switzerland)*, *224*(2), 140–144. 10.1159/000337411

Elston, D. M., Ferringer, T., & Ko, C. J. (2019). *Dermatopathology* (pp. 421–422). Elsevier.

Feng, H., Shuda, M., Chang, Y., & Moore, P. S. (2008). Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science (New York, N.Y.)*, *319*(5866), 1096–1100. 10.1126/science.1152586

Goldstein, R. H., & DeCaprio, J. A. (2019). Merkel cell carcinoma in the HIV-1/AIDS patient. *Cancer Treatment and Research*, *177*, 211–229. 10.1007/978-3-030-03502-0_8

Harms, K. L., Healy, M. A., Nghiem, P., Sober, A. J., Johnson, T. M., Bichakjian, C. K., & Wong, S. L. (2016). Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system. *Annals of Surgical Oncology*, *23*(11), 3564–3571. 10.1245/s10434-016-5266-4

Harting, M. S., Ludgate, M. W., Fullen, D. R., Johnson, T. M., & Bichakjian, C. K. (2012). Dermatoscopic vascular patterns in cutaneous Merkel cell carcinoma. *Journal of the American Academy of Dermatology*, *66*(6), 923–927. 10.1016/j.jaad.2011.06.020

Heath, M., Jaimes, N., Lemos, B., Mostaghimi, A., Wang, L. C., Peñas, P. F., & Nghiem, P. (2008). Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: The AEIOU features. *Journal of the American Academy of Dermatology*, *58*(3), 375–381. 10.1016/j.jaad.2007.11.020

Lemos, B., & Nghiem, P. (2007). Merkel cell carcinoma: More deaths but still no pathway to blame. *Journal of Investigative Dermatology*, *127*(9), 2100–2103. 10.1038/sj.jid.5700925

Lunder, E. J., & Stern, R. S. (1998). Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. *New England Journal of Medicine*, *339*, 1247–1248.

Ma, J. E., & Brewer, J. D. (2014). Merkel cell carcinoma in immunosuppressed patients. *Cancers (Basel)*, *6*(3), 1328–1350. 10.3390/cancers6031328

National Comprehensive Cancer Network. (2019). NCCN clinical practice guidelines in oncology Merkel cell carcinoma. NCCN Guidelines, Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf

Ramahi, E., Choi, J., Fuller, C. D., & Eng, T. Y. (2013). Merkel cell carcinoma. *American Journal of Clinical Oncology*, *36*(3), 299–309. 10.1097/COC.0b013e318210f83c

Sims, J. R., Grotz, T. E., Pockaj, B. A., Joseph, R. W., Foote, R. L., Otley, C. C., Weaver, A. L., Jakub, J. W., & Price, D. L. (2018). Sentinel lymph node biopsy in Merkel cell carcinoma: The Mayo Clinic experience of 150 patients. *Surgical Oncology*, *27*(1), 11–17. 10.1016/j.suronc.2017.10.005

Tello, T. L., Coggshall, K., Yom, S. S., & Yu, S. S. (2018). Merkel cell carcinoma: An update and review: Current and future therapy. *Journal of the American Academy of Dermatology*, *78*(3), 445–454. 10.1016/j.jaad.2017.12.004