The Journal of Foot & Ankle Surgery 53 (2014) 219–225

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Merkel Cell Carcinoma: Case Study and Literature Review

Danae L. Lowell, DPM [1], Jerry Roberts, DPM [2], Prema Gogate, MD [3], Rose Goodwin, DPM [4]

[1] *Staff Surgical Podiatrist, Department of Podiatry Surgery, and Assistant Residency Director, Cleveland Louis Stokes Veterans Affairs Medical Center, Cleveland, OH*
[2] *Submitted during 3rd Year of PMSR/RRA, Cleveland Louis Stokes Veterans Affairs Medical Center, Cleveland, OH*
[3] *Staff Pathologist, Cleveland Louis Stokes Veterans Affairs Medical Center, Cleveland, OH*
[4] *Submitted during 4th Year at Kent State University College of Podiatric Medicine, Kent, OH*

ARTICLE INFO

Level of Clinical Evidence: 4

Keywords:
cancer
cutaneous trabecular carcinoma
lower extremity
neuroendocrine carcinoma
polyomavirus
primary cutaneous
tumor

ABSTRACT

Merkel cell carcinoma is a rare, aggressive, highly metastatic, often fatal, primary neuroendocrine tumor typically located on sun-exposed skin. It is frequently found in white males aged 60 to 70 years. The somewhat typical benign clinical appearance of the lesion can result in a delayed diagnosis, leading to a less than optimal outcome.

According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program from 1973 to 2006, the incidence of Merkel cell carcinoma (MCC) was 0.41 per 100,000 for men and 0.18 per 100,000 for women, and 94.9% of those patients were caucasian (1). The incidence of MCC, most often found on the head and neck regions, tripled from 1986 to 2001, with approximately 1500 cases annually reported in the United States. It is believed that the increased incidence observed during the past 2 decades has been associated with improved diagnostic techniques and an aging population with an overall increased ultraviolet (UV) exposure. Investigators found a 75%, 59%, and 25% 5-year relative survival rate for 1034 patients with localized, regional, and distant MCC disease, respectively (2–4). Before 2007, little was known about this highly malignant skin cancer, which has an age-adjusted incidence of mortality of 0.031/100,000 (5). Since then, significant research and reviews have contributed to the current body of knowledge surrounding MCC. The differential diagnosis for MCC includes lesions that are more common, including basal B-cell carcinoma, squamous cell carcinoma, cutaneous metastatic small cell carcinoma of the lung, small cell cutaneous lymphoma, anaplastic small cell melanoma, Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, epidermoid cyst, amelanotic melanoma, and atypical fibroxanthoma (6–9).

In an effort to review the published data related to MCC, the MEDLINE database was searched for relevant studies. The term "Merkel cell carcinoma" was used as the basis for the searches, and references were included according to their relevance. In 1875, Friedrich Sigmund Merkel originally described the mechanoreceptors we now know as Merkel cells (10). He demonstrated the existence of nondendritic, nonkeratinocyte, touch-sensitive cells (tastzellen) in the skin and suggested that the cells were receptors and transducers of mechanical stimuli to neural impulses (10). After microscopic confirmation of the existence of these cells, the term Merkel cell was coined; and Toker (9) first described MCC in 1972 from his case review. His morphologic description included anastomosing trabeculae, cell nests, and cytoplasmic dense core granules that led to him to describe it as a "trabecular carcinoma of the skin" that he surmised arose from the Merkel cells. The term MCC came from Rywlin (11), who, in 1982, associated the tumor with Merkel cells in the basal layer of the epidermis. Since then, MCC research has led to a better understanding, classification, and treatment of this deadly carcinoma.

MCC typically presents as a singular, "reddish glassy," rapidly growing, pale to violaceous, firm, smooth, nonpainful, shiny nodular dermal lesion that arises 81% of the time in areas of chronic sun (UV radiation) exposure owing to the increased UV exposure to certain areas of the body. Telangiectasia has frequently been noted. Variations exist in which plaque-like lesions are exhibited. Ulcerations are rarely encountered but can be found in more advanced cases (12,13). MCC is rarely found on the oral and genital mucous membranes, where UV exposure is significantly lower. When encountered in these areas, the prognosis has typically been poor (14,15).

Satellite metastases occur early and frequently in cases of MCC and have been found in the skin in 28% of cases, lymph nodes in 27%, liver in 13%, lung in 10%, bone in 10%, and brain in 6% (13). In 2010, Ng et al

Financial Disclosure: None reported.
Conflict of Interest: None reported.
Address correspondence to: Danae L. Lowell, DPM, Department of Podiatry Surgery, Cleveland Louis Stokes Veterans Affairs Medical Center, 10701 East Boulevard, Cleveland, OH 44106.
E-mail address: danae.lowell@va.gov (D.L. Lowell).

1067-2516/$ - see front matter © 2014 by the American College of Foot and Ankle Surgeons. All rights reserved.
http://dx.doi.org/10.1053/j.jfas.2013.10.004

(16) presented the fifth documented case of metastatic MCC to the spine. After resection of the primary lesion in that case, the patient returned with neurologic deficits related to the metastasis. However, postoperative wound healing complications and aspiration pneumonia developed, and the patient died. They also reported occasions in which MCC spinal metastatic lesions were noted, and no primary lesion was ever found. A review of these cases demonstrated similar results and the aggressive nature of MCC (16). Epidemiologic analysis has suggested that the pattern distribution of MCC indicates an association with UV radiation exposure. Of 2384 cases of MCC reviewed by Paulson et al (17), involvement of the left side of the body, predominantly the arm and face, occurred in 52.7% of the cases. An even (50%) distribution was noted on the lower extremities in 571 of the 2384 cases. Their results suggested that driver-side UV exposure might be a contributing factor in the development of MCC. The results from a review of 171 patients with MCC by Koljonen et al (18), in 2012, confirmed left-sided asymmetry in 56% of the cases in sun-exposed areas of the body, although the distribution was equal (symmetrical) in areas typically shaded from the sun. Although UV exposure might be an etiologic culprit in the development of MCC, nonexposed areas are also at risk. In 2011, Iavazzo et al (19) reported a case of vulvar MCC in a 63-year-old female. At the diagnosis, the lesion was 9 cm, and inguinal lymph node metastasis was noted. Fewer than 20 cases of vulvar MCC have been reported.

In addition to UV exposure, immunosuppression has also been determined to be key in the development of MCC. Organ transplant patients receiving immunosuppressive medications and patients with lymphoma, diabetes, or human immunodeficiency virus (HIV) all have a greater incidence of MCC. Engels et al (20) collected data from 309,365 patients with HIV and found 6 cases of MCC, a relative risk of 13.4 (95% confidence interval 4.9 to 29.1) compared with the general population. The results of a study by Tolstov et al (21), in 2011, found no direct correlation between HIV or acquired immunodeficiency syndrome and MCC. This supports the hypothesis that immunocompromise as an associated co-infection transformation was likely. It also suggested that MCC infection, although highly prevalent among adults, is often asymptomatic, indicating that transmission is common but that the actual clinical identification of the carcinoma is rare. The symptoms were similar between patients with HIV who were seropositive and those who were seronegative (21). This research not only supported that immunosuppressive therapy was found to be associated with an increased incidence of MCC but also led to generally a poorer prognosis (22).

Using this information, Heath et al (23) described the mnemonic AEIOU for use when describing the clinical appearance and demographic data associated with MCC. AEIOU stands for an asymptomatic lesion expanding rapidly in a patient with immune suppression, age older than 50 years, with a history of UV exposure to the area. In their study of 195 patients with MCC, 88% were found to be asymptomatic despite rapid growth of the lesion, leading to a median 3-month delay between the initial presentation and diagnosis.

Early lymphovascular invasion might be 1 key to understanding the very aggressive nature of MCC. Kukko et al (24) reviewed 126 MCC samples and found that 93% had intravascular invasion, of which 66% were solely lymphovascular and 3% were only vascular. Although the tumors lacking invasion were typically smaller, lymphovascular invasion was noted in the smallest lesion (0.3 cm in diameter) (24). Possibly contributing to early lymphovascular invasion, Werchau et al (25) investigated the process of lymphangiogenesis in MCC. They found a threefold increase in the mean density of small lymphatic capillaries and a more than eightfold increase in the median ratio of the number of small to large lymphatics compared with the controls (25). The increased lymphangiogenesis occurring with MCC supports a connection between MCC and early lymphovascular invasion and the aggressive nature of MCC.

The morphologic features include an asymmetric dermal distribution in sheets, nests, and serpiginous, diffuse, or trabecular and anastomosing patterns, with frequent subcutis involvement. Small round or oval blue cells, necrosis, nuclei with significant mitotic activity, pagetoid growth, and scant cytoplasm with argyrophil granules have commonly been described (26,27). The papillary dermis, epidermis, and adnexa are usually spared. Three histologic patterns exist, based on the arrangement and appearance of the tumor cells, trabecular, intermediate, and small cell, with intermediate constituting 80% of the 3 types. Although the trabecular pattern has the best prognosis and small cell the worst, frequent mixed and transitional types have been noted, making the histologic prognostic indicators unreliable (28–30).

The typical prognostic factors for determining low, intermediate, and high risk, such as diameter, nodal status, and metastasis, have not held true for MCC (31). Poor prognostic indicators also include the presence of a secondary malignancy such as squamous cell carcinoma or chronic lymphocytic leukemia (32). Other adverse prognostic indicators include disease stage at presentation and male gender. Kaae et al (33) also showed the existence of shared risk factors for MCC and squamous cell carcinoma and chronic lymphocytic leukemia.

Electron microscopy, enzyme, and immunohistochemical assays are used to confirm the expression of chromogranin, synaptophysin, and other neuropeptides. Because a variety of neoplasms display similar characteristics, specific markers for MCC have been determined to distinguish MCC from others. Cytokeratin (CK)20 positivity is specific for MCC and distinguishes it from other small round blue cell tumors. CK20 expression of a paranuclear plaque, a dot-like pattern, has been found in 87% of MCC cases (34,35). Pertinent exclusionary markers for thyroid transcription factor 1 and leukocyte common antigen will largely be diagnostic for MCC (36,37). Thyroid transcription factor-1 and leukocyte common antigen are found in small cell lung carcinoma and lymphoma, respectively, but will be absent in MCC. Neurofilament protein is not found in small cell lung carcinoma and is usually positive in MCC. Endothelial and neuroendocrine markers, including chromogranin and synaptophysin, which are found with differing frequency and intensity, can be used for confirmation (34).

The current recommendations are that once the diagnosis has been confirmed, the next step is to obtain sentinel lymph node biopsy to assist with guiding treatment. Ruan and Reeves (38) in 2009 and Bichakjian et al (39) in 2007 developed treatment algorithms from the highest levels of available published data. Wide local surgical resection, determining the sentinel lymph node status, radiotherapy, chemotherapy and close follow-up to monitor for recurrence have been outlined as methods to evaluate and treat this aggressive carcinoma using multidisciplinary care (38,39).

Experts have agreed that wide local excision with 2- to 3-cm margins is recommended (40–43). Yiengpruksawan et al (43) reported on 70 patients from Sloan-Kettering Cancer Center from 1969 to 1989 and found an overall survival rate of 64% for 5 years. The surgical margins were evaluated in 38 specimens and ranged from 1 to 5 cm, depending on the location. They observed margins of 3 cm or less in 27 (71%) and more than 3 cm in 11 (29%) specimens. Local recurrence was found in 4 of the 27 patients with margins of 3 cm or less compared with none in the 11 patients with surgical margins greater than >3 cm, supporting the recommendation for wide local excision with clear lateral margins greater than 3 cm. However, recurrence and metastatic spread can occur even with larger than recommended excisions, stressing the importance of early recognition and close long-term follow-up. Recurrence rates of 30% to 45% for local disease, 40% to 70% for nodal involvement, and 30% to 50% for distant metastases have been noted (2,44). Medina-Franco et al (45)