Merkel Cell Carcinoma of the Skin

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Merkel cell carcinoma (MCC) is an aggressive skin cancer with high rates of recurrence and distant metastasis. The greatest risk factor for development of MCC is exposure to UV light. Although MCC remains uncommon, its incidence in the United States tripled between 2006 and 2007. Early recognition is key as the stage of disease at diagnosis is linked to survival. However, early disease is often asymptomatic, which can delay diagnosis until regional or distant spread has occurred. MCC lesions can be difficult to distinguish clinically from benign or other less malignant lesions and histologically from other small blue cell tumors. Thus, diagnosis relies on immunohistochemical analysis. Surgery is the main treatment modality, and most patients undergo radiotherapy as well. Further research is required to formulate evidence-based management guidelines for patients with MCC who might benefit from adjuvant chemoradiotherapy.

Merkel cell carcinoma (MCC), also known as neuroendocrine carcinoma of the skin, is an uncommon, highly aggressive type of skin cancer. MCC was first reported in 1972 by Toker, who used the term "trabecular carcinoma" of the skin to describe a poorly differentiated carcinoma of the dermis and subcutaneous tissue in 5 patients.[1] MCC predominately occurs in elderly patients. The average age of patients at diagnosis is 69 years, and most patients (> 95%) diagnosed with MCC are older than 50 years.[2,3] Although MCC is a rare neoplasm with an approximate age-adjusted incidence of 2.4 cases per 100,000 person-years,[4] the number of newly reported cases has dramatically increased over the past few years, with 1500 new cases reported in 2007 as compared with 500 in 2006.[3,4] The overall 5-year survival rate ranges from 30% to 64%, with the stage of disease at time of diagnosis strongly predicting survival.[2] In patients with small tumors and localized disease, 5-year survival may exceed 90%,[2] while half of patients with advanced disease will survive only 9 months.[5] Since patients with clinically localized disease have the best chance of cure, early recognition and prompt treatment are essential to improve outcomes in patients diagnosed with MCC.

RISK FACTORS

UV radiation and immunosuppression have been implicated in the pathogenesis of MCC. MCC tumors occur most frequently in areas of the skin that are exposed to the sun, and the incidence of MCC is higher in geographical regions with increased sun exposure as measured by the UV-B solar index.[6] In addition, a 100-fold increased incidence of MCC has been reported in patients treated with methoxsalen and UV-A for psoriasis.[7] However, other factors contribute to its development since MCC tumors do arise in areas without sun exposure.[4,8–10] For example, MCC is also associated with previous irradiation and exposure to radiant infrared heat.[6,11–16] Immunosuppression, regardless of the etiology, also significantly contributes to the pathogenesis of MCC, with a 10- to 40-fold increased incidence observed in solid organ recipients[17–20] and a 13-fold increase in HIV-positive patients as compared with the general population.[18,21] Immunocompromised patients not only experience a higher incidence of MCC, but also typically present at a younger age (53 yr versus 74 yr) and at a more advanced stage (68% have nodal disease versus 39% of immunocompetent patients with MCC)[4,19,20] and have a higher disease-specific mortality rate (56% versus 25%–35% in immunocompetent patients).[19] There is also a higher prevalence of some malignancies in patients diagnosed with MCC, such as small cell lung cancer (SCLC), chronic lymphocytic leukemia, and breast and ovarian cancer.[22] The presence of these neoplasms, whether they appear before, after, or simultaneously with MCC, is associated with a higher MCC-specific mortality.[22]

Cytogenic analysis has shown that MCC shares chromosomal abnormalities with melanoma, neuroblastoma, and SCLC.[23,24] Although there are no consistent chromosomal abnormalities, the most common alteration occurs in the short arm of chromosome 1, similar to that seen in some melanomas and neuroblastoma. This differs from SCLC, in which the majority of cases have abnormalities in chromosome 3p21.[25]

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TAKE HOME POINTS

- Merkel cell carcinoma (MCC) typically presents as a progressively enlarging, solitary, erythematous nodule located in sun-exposed regions. The nodule is usually red or violaceous with a shiny surface and often with overlying telangiectatic features.
- MCC can resemble other types of skin cancer, particularly basal cell carcinoma, but also amelanotic melanoma, small cell carcinoma, and cutaneous lymphoma.
- Tumor characteristics that may aid in suspecting MCC are summarized with the mnemonic "AEIOU" (Asymptomatic, Expanding rapidly, Immune suppressed, Older than age 50 years, UV exposed).
- Although MCC typically presents as a small primary tumor, occult or overt metastases are detected in 10% to 30% of cases at the time of diagnosis.
- Because MCC closely resembles other small round blue tumors (eg, small cell lung carcinoma) on staining, a broad immunopanel is typically required to rule out these entities.

DIAGNOSIS

Clinical Presentation

In most cases, MCC tumors present as a progressively enlarging, solitary, erythematous nodule located in sun-exposed regions.[2] The usual appearance of MCC is a red or violaceous nodule with a shiny surface, often with overlying telangiectatic features (**Figure 1**).[26] The head and neck are the primary sites of involvement in more than half of patients,[27] followed by the extremities in 40% and trunk in less than 10%.[28–33] On the face, the eyelids are involved most frequently (**Figure 2**).[34] Amelanotic melanoma, small cell carcinoma, basal cell carcinoma, and cutaneous lymphoma can present with clinical features similar to MCC. Because MCC is rare and can resemble these skin cancers as well as some benign skin lesions on initial presentation, physicians often do not suspect MCC as the primary diagnosis. Tumor characteristics that may aid in suspecting and diagnosing MCC are summarized as "AEIOU" (Asymptomatic, Expanding rapidly, Immunosuppressed, Older than age 50 years, UV exposed).[35] Patients who present with a suspicious skin lesion should undergo a complete examination of the skin and regional lymph nodes as well as biopsy. The AEIOU criteria also may be helpful in deciding when to perform a biopsy.

Figure 1. Merkel cell carcinoma on the cheek. (Image courtesy of Shane Chapman, MD, Department of Dermatology, Dartmouth Hitchcock Medical Center, Lebanon, NH.)

Pathology

MCC seems to be derived from mechanoreceptors called Merkel cells, which are located in the basal cell layer of the skin and in the outer root sheath of the hair follicle at sites of high hair density as well as in the glabrous epithelium of digits and lips and in the oral cavity and penis.[10,36–38] MCC tumors are composed of small round blue cells and are often confused with other small blue cell tumors on light microscopy, particularly metastatic SCLC. Other malignancies that are histologically similar to MCC include extrapulmonary neuroendocrine tumors, neuroblastoma, basal cell carcinoma, small cell amelanotic melanoma, lymphoma, Ewing's sarcoma, and squamous cell carcinoma of the skin.[2,24] Because metastatic SCLC and other small round blue tumors closely resemble MCC on hematoxylin and eosin staining, diagnosis based on histology alone is not possible and a broad immunopanel is typically required to rule out these entities.[39–44] In particular, MCC can now be more easily distinguished from histologically similar tumors by the use of the immunohistochemical marker cytokeratin-20 (CK-20).[2,39–42] Before CK-20 immunohistochemistry was available, electron microscopy was required to make an accurate MCC diagnosis. Indeed, 66% of MCC cases in one series would have been misdiagnosed had electron microscopy not been performed to demonstrate the characteristic "neurosecretory granules within cytoplasmic extensions."[39]

Immunohistochemistry

MCC is unique in that it expresses both epithelial and neuroendocrine markers and that it microscopically exhibits a characteristic perinuclear dot-like pattern with low-molecular-weight cytokeratins, especially CK-20,

on examination with keratin immunoperoxidase staining.[39–44] CK-20 is a sensitive marker of MCC, staining positive in 89% to 100% of patients with either primary or metastatic disease. However, CK-20 expression by SCLC and lack of CK-20 expression in MCC have also been reported.[39–44] Thus, the immunopanel should also include thyroid transcription factor-1, which is expressed in most SCLC (83%–100%) but is consistently negative in MCC. Furthermore, the majority of MCC tumors express Kit receptor tyrosine kinase (CD-117), but it can also be expressed in SCLC. Given the overlap of marker expression in MCC and SCLC, diagnosis does not rely on the presence or absence of any these markers individually but on a combination of markers. **Table 1** delineates the immunohistochemical stains routinely used to differentiate MCC from other cytomorphologically similar tumors.

Figure 2. Merkel cell carcinoma of the eyelid. (Image courtesy of Shane Chapman, MD, Department of Dermatology, Dartmouth Hitchcock Medical Center, Lebanon, NH.)

STAGING AND PROGNOSIS

A staging system developed at Memorial Sloan-Kettering Cancer Center (MSKCC) in the 1980s[45] was recently revised by Allen and colleagues[46] into a 4-stage system that classifies patients based on the size of the primary tumor and the presence or absence of lymph node involvement and distant metastases (**Table 2**). In general, MCC should be regarded as a systemic disease due to its highly aggressive nature. Although MCC typically presents as a small primary tumor, occult or overt metastases are detected in 10% to 30% of cases at the time of diagnosis.[36] In 2 large Australian series involving 33 and 54 patients, nodal metastases were present in 33% and 40% of patients, respectively.[47,48] However, another series with 22 patients reported nodal metastases at presentation in only 11% of patients.[49] Patients may also present with metastatic nodal disease without an obvious primary index lesion. Two studies reported metastatic nodes from an unknown primary site at the time of diagnosis in 19% of 86 patients[50] and in 16% of 33 patients.[47]

Once the pathology confirms the presence of a small blue cell tumor, clinicians need to consider the possibility of metastatic SCLC, especially in smokers. These patients should have chest imaging to exclude lung cancer or the possibility of pulmonary metastases.[51] Patients presenting with clinical nodal metastases should also have computed tomography (CT) scans of the abdomen for complete staging as well as CT of the head and neck if the primary tumor is located there.[51] Positron emission tomography/CT is sometimes used for staging, but its role is not yet established due to a lack of controlled studies. This modality may become a valuable tool in evaluating and staging of future cases as more data become available.

As with other malignancies, the natural history of MCC varies depending on the stage of disease at presentation. Localized primary tumors can be indolent and well controlled by local excisional surgery alone, while prognosis is poor if systemic disease is present.[2,31,32] In a series of 251 patients with MCC treated at MSKCC between 1970 and 2002, the overall 5-year disease-specific survival was 64%.[46] The 5-year survival rate in patients with pathologically proven absence of lymph node disease was 97% as compared with a 52% rate in those with pathologically positive nodes. The disease recurs in approximately 50% of patients after initial resection of the primary tumor.[46]

TREATMENT

Therapy for MCC is multimodal and interdisciplinary. It is important to note that a standard treatment protocol for MCC has not been established because data from large prospective randomized trials are not available to verify the validity of any prognostic features or treatment outcomes.[52] As a result, National Comprehensive Cancer Network (NCCN) guideline recommendations are based on trends documented by small studies, meta-analyses, and clinical experience and reflect the variability among participating NCCN institutions in treating MCC, including the use of sentinel lymph node biopsy (SLNB), adjuvant radiotherapy, and adjuvant chemotherapy.

Surgery is the primary treatment modality for clinically localized disease. The goal of surgical excision is to obtain clear margins when clinically feasible, and the gold standard in general has been wide excision. More recently, Mohs micrographic surgery has been used as an alternative method and has resulted in good locoregional control comparable to wide excision.[53]

MCC is known to be highly radiosensitive, and a

Table 1. Immunohistochemical Staining Patterns of Small Round Blue Cell Tumors of the Skin

	CK-20	CK-7	CD-99	NSE	NFP	EMA	TTF-1	LCA	S100	BER-EP4
Merkel cell carcinoma	+	–	+/–	+	+	+	–	–	–	+
Small cell lung cancer	Rare	+	+/–	+	+/–	+	+	–	–	–
Small cell amelanotic melanoma	–	–	–	+	–	–	–	–	+	–
Lymphoma/leukemia	–	–	+/–	–	–	+/–	–	+	–	–
Ewing's sarcoma	–	–	+	+	+/–	+/–	–	–	+/–	–
Carcinoid	+	+/–	+/–	+	–	+/–	+/–	–	–	–
Basal cell carcinoma	–	+/–	–	–	–	–	–	–	–	+

CD-99 = cluster-of-differentiation antigen 99; CK = cytokeratin; EMA = epithelial membrane antigen; LCA = leukocyte common antigen; NFP = neurofilament protein; NSE = neuron-specific enolase; TTF-1 = thyroid transcription factor-1.

Table 2. Memorial Sloan-Kettering Cancer Center Staging System for Merkel Cell Carcinoma

Stage		Localized Disease	Lymph Node	Metastasis
I	Primary lesion < 2 cm	+	–	–
II	Primary lesion > 2 cm	+	–	–
III	Positive lymph node	+/–	+	–
IV	Distant metastasis	+/–	+/–	+

Adapted from Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol 2005;23:2301.

number of studies have shown a benefit of adjuvant radiotherapy following excision to reduce locoregional recurrence.[46–48,50,54–60] In an Australian study, 10 of 16 patients treated with surgery alone experienced a locoregional relapse as compared with none of 11 treated with surgery and adjuvant radiotherapy.[47] In a series of patients treated with surgery alone (n = 37), most (89%) experienced local (9 of 37), locoregional (7 of 37), or regional (17 of 37) relapse, while only 5 of 12 (42%) patients treated with surgery and radiotherapy developed recurrent disease, including 1 with a distant failure.[48] A Westmead Hospital (n = 86) study found regional relapse rates of 37% in patients treated with surgery (including 7 with nodal dissections for clinical disease) versus 18% in those treated with surgery and adjuvant radiotherapy.[50] The authors of another series reported a 100% relapse rate (mostly regional) in 38 patients treated with surgery alone as compared with only 29% in those receiving adjuvant radiotherapy.[59] In a similar study of 34 patients treated with wide local excision, 59% experienced a regional relapse as compared with a 27% rate in 26 patients treated with local surgery and adjuvant radiotherapy (46–66 Gy to primary site and draining lymphatics).[60] These data show that adjuvant radiotherapy is essential and life-saving and support its use in most patients with MCC. In addition, a study by Tsang and colleagues[61] demonstrated that delaying radiotherapy for treatment of MCC is associated with a high risk of progression, with 11 of 27 patients developing progressive disease after a median delay of 24 days. Based on these results, the authors recommend that patients with MCC should be assigned a high priority for commencement of radiotherapy.[61]

SLNB prior to wide excision is used in some institutions to determine the presence or absence of lymph node disease in patients without clinical evidence of lymph node involvment, information that can be used to select patients for elective node dissection for regional control and to make decisions regarding the extent of radiotherapy.[2,54] If the sentinel node is negative for micrometastatic disease, postoperative radiotherapy to the primary site only may be appropriate, while a positive sentinel node is followed-up with completion lymph node dissection and adjuvant radiotherapy. However, it remains controversial whether SLNB provides a survival benefit,[52] and use of this technique in treating MCC should be considered investigational at this time.

Adjuvant chemotherapy has been considered in MCC given the high rate of nodal relapse (50%–75%) and systemic relapse (30%–50%) after local treatment.[26] However, only retrospective data regarding adjuvant therapy are available. These studies do not show that adjuvant chemotherapy prolongs survival and are insufficient to assess whether it positively impacts progression-free or overall survival.[17,46,54–56] It has been suggested that chemotherapy should be withheld for palliation in patients in whom surgery and radiation

are no longer an option because, as with many other malignancies, MCC seems to gain broad resistance to chemotherapeutic agents after an initial course of chemotherapy.[57]

Follow-up Care

NCCN guidelines recommend that patients undergo a complete examination following treatment for MCC, including whole body skin examination as well as regional lymph nodes, every 1 to 3 months for the first year, every 3 to 6 months for the second year, and annually thereafter.[52] These guidelines apply to patients who are node-negative or -positive as well as those who have disseminated disease. Given the high risk for recurrence in MCC, diligence in follow-up is required.

CONCLUSION

MCC is an increasingly common and extremely aggressive skin malignancy. Because the early course of MCC is asymptomatic, diagnosis may be delayed until regional lymphadenopathy and distant metastases have developed. Several tumor characteristics that may aid the clinician in suspecting MCC, summarized as AEIOU, have been identified. In addition, a variety of skin lesions share similar features with MCC, and these criteria also may be helpful in deciding when to perform a biopsy. The treatment and outcome reported in mostly small retrospective studies is varied, although patients treated with a multimodality approach appear to have a better outcome. Debate continues regarding the optimal approach to treating patients with MCC, and discussion revolves mainly around the efficacy of postoperative adjuvant treatment. Further research is required to formulate evidence-based management guidelines for patients with MCC. **HP**

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