Merkel Cell Carcinoma: A Review of Current Advances

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Key Words
Merkel cell carcinoma, polyomavirus, sentinel lymph node biopsy, radiotherapy, immunohistochemical analysis

Abstract
Merkel cell carcinoma (MCC) is a rare but aggressive cutaneous malignancy of neuroendocrine origin. Its incidence has tripled over the past 15 years. This article reviews the recent advancement in diagnosis, discoveries in pathogenesis, and updates in management. The acronym, AEIOU, has been proposed to aid in clinical identification. In addition to cytokeratin 20, newer immunohistochemical stains (in particular thyroid transcription factor-1 and neurofilament protein) have proven to be essential in pathologic diagnosis. Although immune suppression and ultraviolet radiation have long been associated with the MCC oncogenesis, recent studies also show involvement of a new polyomavirus and bcl-2. Several tumor classifications have been published in the literature, with the 4-tiered system from Memorial Sloan-Kettering Cancer Center the most widely used. A similar classification with additional distinctions among nodal disease is being constructed. A multidisciplinary treatment algorithm is recommended for MCC. Surgical excision with adjuvant radiotherapy (RT) is indicated for localized tumors. RT is favored over complete lymph node dissection and chemotherapy for regional lymph node involvement. For distant metastasis, management should be individualized with a combination of palliative surgery, RT, and chemotherapy. (JNCCN 2009;7:333–339)

Epidemiology
Compared with other cutaneous malignancies, the incidence of MCC is low but increasing at a rapid rate. Over the past 15 years, its incidence has tripled from 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001. The annual rate of increase during this period was 8%. In a direct comparison, age-adjusted incidence rates for melanoma increased from 12.2 cases per 100,000 in 1986 to 18.24 cases per 100,000 in 2001. The rate of increase per year for melanoma over this same period was only 3%. An estimated 1500 new cases of MCC will occur this year in the United States, which exceeds the incidence of cutaneous T-cell lymphoma but is still 50-fold fewer than those of melanoma. MCC predominantly affects the older population, with 90%...
and 76% of patients older than 50\textsuperscript{e} and 65 years,\textsuperscript{f} respectively. The median age of onset ranges from 69 to 74 years.\textsuperscript{6-9} Approximately 94% to 98% of individuals are white,\textsuperscript{6,7,8} and most larger studies also show a moderate male predominance.\textsuperscript{3,6-9}

**Clinical Presentation**

The clinical features of MCC are nonspecific. Most commonly, it presents as an asymptomatic erythematous to violaceous nodule on sun-exposed skin. The diameter of the primary tumor varies, from less than 1 cm in 21.3%, to between 1 to 2 cm in 43.3%, and greater than 2 cm in 35.3%. Ulceration occasionally presents. Many tumors show rapid growth within the first 3 months (63%). At biopsy, most lesions are clinically considered benign (56%), with cystic acne the single most likely diagnosis (32%). Because MCC prognosis is highly associated with extent of disease at presentation, Heath et al.\textsuperscript{6} devised an acronym: AEIOU (asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than 50 years, and ultraviolet-exposed site on a person with fair skin) to aid in the clinical diagnosis. Based on their study of 195 cases, 89% of patients with primary MCC had 3 or more of the features.

The most common location of the primary lesion is the head and neck region (29%–48.3%), followed by extremities (33%–45%) and trunk (7%–23%).\textsuperscript{6-9} Surveillance, Epidemiology, and End Results (SEER) data also showed that incidence of head and neck tumors increased with increasing age: 29.8% in men younger than 65 years, 50% in those between 65 and 74 years, and 54.7% in men older than 75 years. Rare but highly aggressive cases have also been reported on the oral and genital mucosa.\textsuperscript{10,11}

MCC is associated with a high rate of metastasis, with regional lymph node involvement in 24% to 37.4% and distant metastasis in 5.9% to 8% of cases.\textsuperscript{6,8,12} The most frequent sites of metastasis are the lymph nodes (29%–60.1%), followed by distant skin (27.7%–30.3%), lung (10%–23.4%), central nervous system (0%–18.4%), bone (9.9%–15.4%), and liver (0%–13.4%).\textsuperscript{8,9,13} Metastatic MCC without a primary lesion occurred at a frequency of 3% to 19%.\textsuperscript{9,14}

Despite its aggressive nature, 20 cases of spontaneous regression were reported in the literature as of June 2008. They share 3 common features: 1) female predominance (70%), 2) head and neck involvement (95%), and 3) fast rate of regression usually within months.\textsuperscript{15-19} A cell-mediated immune response has been postulated as a likely mechanism of action.\textsuperscript{20-24}

**Histopathology**

MCC typically appears as an ill-defined multinodular dermal tumor with frequent extension into subcutaneous fat and muscle. Ulceration is present in approximately 20% of cases.\textsuperscript{25} Epidermal involvement in form of epidermotropism is uncommon, and only 3 cases of tumor involvement limited to the epidermis or MCC in situ have been reported in the literature. All in situ lesions are associated with squamous cell carcinoma.\textsuperscript{26}

The tumor nodule itself is composed of small, round to oval, blue cells of uniform size with a vesicular nucleus and multiple small nucleoli. Common features include high mitotic rate, vascular invasion, tumor necrosis, and perineural invasion. Three distinct but often admixed histologic patterns have been recognized, with intermediate pattern the most common. The small cell pattern is virtually indistinguishable from other small cell tumors, especially small cell carcinoma of the lung (SCCL). The trabecular pattern is the least common type and usually never stains MCC. Two immunoperoxidases, thyroid transcription factor-1 (TTF-1) and neurofilament protein, were identified and proven useful in distinguishing MCC from SCCL. TTF-1 is positive in 83% to 100% of SCCL but is consistently negative in MCC. Neurofilament protein is less sensitive than CK20 in staining MCC (63%–100%) but almost never stains SCCL.\textsuperscript{28-30} Similarly, appropriate combinations of immunoperoxidase stains can differentiate MCC from other small cell tumors (Table 1).\textsuperscript{10}
**Pathogenesis**

The exact origin of MCC still remains elusive. Nevertheless, strong evidence supports the role of immunosuppression in its pathogenesis. Occurrences have been reported in association with solid organ transplantation, bone marrow transplantation, chronic immunosuppressive therapy for rheumatoid arthritis, chronic lymphocytic leukemia, and HIV infection. In a recent study of 195 cases, 7.8% of individuals had some form of immune impairment, which is a 16-fold overrepresentation of immunosuppression compared with the general United States population. In another review of 1024 cases, 14.5% of patients had undergone or were undergoing some form of immunosuppressive therapy. The ratio of post-transplant melanoma to MCC is 6:1, whereas it is 65:1 in the general population. Furthermore, the relative risk for MCC is 13.4 (95% CI, 4.9–29.1) in patients infected with HIV compared with the general population. These results suggest that immune suppression increases the risk for developing MCC.

Evidence is also plentiful for ultraviolet radiation (UV) as a pathogenic factor in MCC. Most tumors are located in sun-exposed anatomic sites. SEER data from different geographic locations showed a correlation between UVB indexes and regional differences in MCC incidence. Lunder and Stern reported a 100-fold increase in occurrence of MCC in patients with psoriasis treated with both UVA and methoxsalen. Multiple reports also described the concurrence of MCC with squamous and basal cell carcinoma. In addition, p53 mutation of UVB signature-type has been detected in MCC tumors, confirming the close association of UV exposure and MCC development.

Most recently, data have suggested a viral origin in the pathogenesis of MCC. Feng et al. identified a new polyomavirus, which they appropriately named *Merkel cell polyomavirus* (MCV). MCV sequences were detected in 8 of 10 (80%) MCC tumors but only 5 of 59 (8%) control tissues from various body sites and 4 of 25 (16%) control skin tissues. In 6 of 8 MCV-positive MCCs, viral DNA was integrated within the tumor genome in a clonal pattern, suggesting that MCV infection and integration preceded clonal expansion of the tumor cells. Presence of MCV in MCC tumor cells was also confirmed by others. Additional studies by Shuda et al. showed that MCV-infected MCC tumor cells undergo active mutation to prevent autoactivation of integrated virus replication that would be harmful to cell survival. This further confirms MCV's direct role in MCC oncogenesis and not as an incident infectious agent.

On a molecular level, results from cytogenetic research hypothesized a candidate tumor suppressor gene on the short arm of chromosome 1 (1p). In one study, 40% of MCC tumors had structural abnormalities on 1p. Another study showed that 73% of tumors had loss of heterozygosity on 1p. However, no conclusive candidate gene has been identified. Nine known cancer-associated genes—p53, Ras, B-Raf, MAP kinase, Wnt, c-Kit, PTEN, bcl-2, and platelet-derived growth factor receptor—have been examined for their possible role in MCC oncogenesis. Of these, only the studies on bcl-2 had strong supporting evidence. A high expression of bcl-2 was found in 75% of MCC tumors (n = 20). Also, bcl-2 antisense oligonucleotide administration reduced tumor size in an SCID mouse/human xenograft model.

**Diagnosis**

Recognition of MCC requires a high index of suspicion because it does not have distinctive clinical features. MCC is more likely to resemble a benign lesion (56%) than a malignant growth (32%). The recently

<table>
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<tr>
<th>Tumor</th>
<th>CK20</th>
<th>CK7</th>
<th>NSE</th>
<th>NFP</th>
<th>S100</th>
<th>LCA</th>
<th>CD99</th>
<th>TTF–1</th>
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<tbody>
<tr>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Rarely +</td>
<td>–</td>
</tr>
<tr>
<td>SCCL</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–/–</td>
<td>–</td>
<td>Rarely +</td>
<td>+</td>
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<tr>
<td>Lymphoma</td>
<td>–</td>
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<td>MPNT</td>
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<td>Rarely +</td>
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**Table 1 Immunohistochemical Stains That Differentiate MCC From Other Small Cell Tumors**

Abbreviations: CK20, cytokeratin 20; LCA, leukocyte common antigen; MCC, Merkel cell carcinoma; MPNT, malignant primitive neuroectodermal tumor; NFP, neurofilament protein; SCCL, small cell carcinoma of lung; TTF-1, thyroid transcription factor 1.
proposed acronym, AEIOU, should aid in the clinical identification.\textsuperscript{6} The definitive diagnosis, nevertheless, requires histologic examination and display of characteristic immunohistochemical profiles.

Two major staging systems have been reported in the literature: the Memorial Sloan-Kettering Cancer Center (MSKCC) staging system for patients with MCC and the American Joint Committee on Cancer (AJCC) TNM staging criteria for non-melanoma skin cancer. The MSKCC staging system was first reported in 1991 as a 3-tiered system based on nodal involvement (stage I = node-negative; stage II = node-positive; stage III = distant metastasis).\textsuperscript{51} Subsequently, a follow-up study from MSKCC reported the diameter of primary tumor (< 2 or $\geq 2$ cm) as an addition predictor of survival in patients with node-negative MCC.\textsuperscript{52} The MSKCC system was then formally revised to a 4-tiered system in 2005 (Table 2)\textsuperscript{8} and is now the most widely used staging system, even adopted by the National Cancer Institute. Clark et al.\textsuperscript{53} described a revision of this system, which they believed was more predictive of disease-specific survival. They changed the cut-off diameter of primary tumor from 2 to 1 cm and placed larger primary tumor (diameter $> 1$ cm) at a higher stage than small primary tumor with a positive regional lymph node.\textsuperscript{53}

However, AJCC staging criteria, reported in the 6th edition in 2002, upgraded primary tumor of any diameter size with deeper extradermal involvement to stage III. In a direct comparison, the MSKCC staging system seemed to better risk-stratify MCC than the AJCC staging criteria within the SEER population (1988–2002).\textsuperscript{54} Neither system, however, differentiates method of detecting nodal involvement—clinical versus pathologic. A new classification system is currently being constructed for the 7th edition of the AJCC staging manual to be published in 2009. This new system will be similar to the 4-tiered MSKCC staging system, but will also distinguish macroscopic (clinical) versus microscopic (pathologic) nodal disease.\textsuperscript{55}

Application of tumor thickness in MCC similar to that of Breslow depth in melanoma has been investigated but with conflicting results. Multiple studies failed to detect a correlation between tumor thickness and survival, and between tumor thickness and metastasis.\textsuperscript{56–58} Sample size of these studies was relatively small (largest n = 60). A newly published review of 156 patients with MCC, however, determined that tumor thickness, lymphovascular invasion, and tumor growth pattern are the 3 histologic factors of prognostic significance.\textsuperscript{59,60} Additional high-powered studies are needed to validate the usefulness of Breslow depth in MCC.

Status of regional lymph node involvement is essential for accurate MCC tumor classification and treatment indications and is the most reliable prognostic factor in the literature. MCC is twice as likely to involve regional lymph nodes than melanoma (~30% vs. ~15%).\textsuperscript{55,60} Studies have shown that 23% to 32% of patients with no palpable lymph node clinically will have a positive SLNB.\textsuperscript{8,60} Therefore, SLNB is indicated for patients who present without palpable lymphadenopathy clinically.\textsuperscript{60}

Efficacy of CT in detecting nodal disease has also been examined. CT had a very low sensitivity (20%) in detecting regional lymph node involvement. It did, however, have a high sensitivity (100%) in detecting distant metastasis. Consequently, CT should be considered in all patients with positive regional lymph node clinically will have a positive SLNB.\textsuperscript{8,60} Therefore, SLNB is indicated for patients who present without palpable lymphadenopathy clinically.\textsuperscript{60}

**Table 2** Memorial Sloan-Kettering Cancer Center Staging System for Patients With Merkel Cell Carcinoma

<table>
<thead>
<tr>
<th>TNM Scores</th>
<th>Stages</th>
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<tr>
<td>T1 = primary tumor &lt; 2 cm</td>
<td>I</td>
</tr>
<tr>
<td>T2 = primary tumor $\geq 2$ cm</td>
<td>II</td>
</tr>
<tr>
<td>N0 = negative regional lymph nodes</td>
<td>III</td>
</tr>
<tr>
<td>N1 = positive regional lymph nodes</td>
<td>IV</td>
</tr>
<tr>
<td>M0 = no distant metastasis</td>
<td>Any T, N0, M0</td>
</tr>
<tr>
<td>M1 = distant metastasis present</td>
<td>Any T, N1, M0</td>
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</tbody>
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**Treatment**

MCC is well known for its high rate of recurrence and mortality. Therefore, a multidisciplinary approach is currently recommended for its management. Similar to melanoma, treatment varies based on tumor stage.

For localized disease, surgical excision with adjuvant radiotherapy (RT) is recommended. Wide
local excision (WLE) with a 2- to 3-cm surgical margin has been the general practice, but the optimal surgical margin remains controversial. WLE alone has been associated with local and regional recurrence rate of 6% to 100%, and 37% to 85%, respectively. Mohs surgery attained more promising results, with local and regional recurrence rates of 0% to 16% and 28% to 33.3%, respectively. Nevertheless, the most significant improvement in recurrence rate is accomplished with addition of RT. Patients treated with WLE and RT were 3.7 times less likely to develop local recurrence and 2.9 times less likely to experience regional relapse. Likewise, combination of Mohs surgery and RT reduced local and regional recurrence to 0% and 15%, respectively. RT as a monotherapy has also been reported to be as effective as combination therapy and should be used whenever extensive surgical excision is contraindicated. Furthermore, a recent analysis of SEER registry from 1973 to 2002 showed that adjuvant RT improved survival in patients with MCC.

For regional lymph node involvement, a shift has occurred in the current practice from the traditional complete lymph node dissection (CLND) to nodal RT. CLND was considered less efficacious and more toxic than that of RT. Gupta et al. illustrated that nodal RT improved relapse-free survival from 0% in patients who did not undergo RT to 60% in those who did. The benefit of adding nodal RT to individuals with a negative SLND was unclear. Although there was a trend for improved relapse-free survival, it was not statistically significant (70% vs. 90%; $P = .26$). Nevertheless, considering the high likelihood of lymph node involvement in MCC, nodal RT should be considered in all patients unable to tolerate SLNB. Also, adjuvant chemotherapy is no longer recommended for treating nodal disease. Chemotherapy was associated with considerable morbidity (60% with neutropenia, 40% with sepsis) and a higher mortality rate (decreased survival from 60%–40%).

Treatment of distant metastasis requires a combination of palliative surgery, RT, and chemotherapy.
Individualized management with discussion at a multidisciplinary tumor board is highly recommended. Figure 1 shows an algorithm for managing MCC based on consensus from 20 cancer centers in the United States.8

**Prognosis**

MCC is associated with a high mortality rate (33%), more than twice that of melanoma (15%).8 Based on the 4-tiered MSKCC staging system, the 5-year disease-specific survival rate was 64%. Disease stage was the only independent predictor of survival (stage I = 81%; stage II = 67%; stage III = 52%; and stage IV = 11%).

**Conclusions**

Over the past decade, significant advances have been made in the diagnosis, pathogenesis, and treatment of MCC. Even so, its exact etiology remains elusive and controversies remain over optimal management. Because published results on MCC are often based on small retrospective studies, evidence conflicts. A multicentered prospective trial will help improve understanding of MCC oncogenesis and formulate an optimal treatment plan.

**References**


