REVIEW ARTICLE

Merkel Cell Carcinoma

By Wolfram Goessling, Phillip H. McKee, and Robert J. Mayer

IN 1875, FRIEDRICH Sigmund Merkel (1845-1919) described a unique epidermal nondendritic, nonkeratinocyte cell, which he called a tactile cell (Tastzelle). This cell, now bearing his name, was thought to be a primary touch receptor.[1] Merkel cells are now generally believed to be primary neural cells, found as single cells within the basal layer of the epidermis or grouped together as a component of the tactile hair disc of Pinkus in the hair-bearing skin of mammals, functioning as slowly adapting type I mechanoreceptors.[2,3] Their origin from the neural crest is supported by recent interspecies embryonic transplantation models in birds,[4] but other authors invoke an epidermal origin from keratinocytes.[5,6] In 1972, Toker[7] described five cases of a trabecular cell carcinoma of the skin, which was initially thought to be derived from sweat glands. However, in 1978 Tang and Toker[8] found dense-core granules typical of Merkel cells and other neuroendocrine cells on electron microscopy in these trabecular tumors, suggesting an origin from the Merkel cell. Also called (neuro)endocrine cancer of the skin or small-cell carcinoma of the skin, the name Merkel cell carcinoma (MCC) was suggested by De Wolf-Peeters et al[9] in 1980. Approximately 2,000 cases have thus far been reported, and this disease has not previously been the subject of a comprehensive review in the oncology literature.

BIOLOGIC FEATURES

Epidemiology

MCC is a rare cutaneous neoplasm of the elderly population with estimated 470 new cases in the United States each year; this incidence figure compares with 31,000 new cases of melanoma annually. Miller and Rabkin[10] calculate the annual incidence based on Surveillance, Epidemiology, and End-Results data as 0.23 per 100,000 for whites, which is similar to an estimate using the defined patient population of the Mayo clinic.[11] The incidence among blacks seems lower (0.01 cases per 100,000), only a few cases having been reported in this population group.[12-14] Although most studies show a male predominance, with SEER data suggesting a ratio of 2.3:1,[10] other case series demonstrate a slightly higher incidence in women.[15,16] MCC is a disease of the elderly with an average age at the time of diagnosis of 69 years;[15-19] only 5% of all reported patients have been diagnosed below the age of 50 years,[10] with a reported age range of 7 to 104 years.[20,21]

Clinical Presentation

At the time of diagnosis, patients typically present with a flesh-colored, red, or blue, firm, nontender intracutaneous mass that has grown rapidly over a few weeks to months and may ulcerate.[22,23] Most commonly, the tumor is nodular but may also have a plaque-like appearance (Fig 1). Tumor size ranges from 2 to 200 mm but is most commonly less than 20 mm. It affects primarily the sun exposed areas of the skin, with approximately 50% of all tumors occurring in the face and neck; 40% appear on the extremities, and 10% on the trunk and genitals.[15,24-30] In the face, the eyelids are involved frequently.[31-33] Rare occurrences in sun-protected areas, such as oral mucosa,[34] vulva,[35] and penis[36] have been described. The tumor spreads frequently; common secondary sites include the skin (28%), lymph nodes (27%), liver (13%), lung (10%), bones (10%), and brain (6%).[14] Symptoms are typically local and related to tumor growth or lymph node involvement. Superior vena cava syndrome secondary to obstruction by tumor mass[37] as well as paraneoplastic neurologic complications[38] have been reported.

Staging and Prognosis

Most patients with MCC present with localized disease (70% to 80%); 10% to 30% of patients have regional lymph node involvement, and 1% to 4% have distant metastases at the time of initial presentation.[15,22,23,26] There is no accepted staging system for MCC, but several investigators have adopted a simple system proposed by Yiengpruksawan et al:[22] stage I, localized skin disease (stage IA $\leq$ 2 cm, IB $>$ 2 cm); stage II, regional lymph node disease; and stage III, metastatic disease. Purported favorable prognostic factors include primary tumor location in the head and neck region and without involvement of regional lymph nodes,[16,22] tumors $\leq$ 2 cm in size (stage IA),[39] and female sex.[16,23,26,40]

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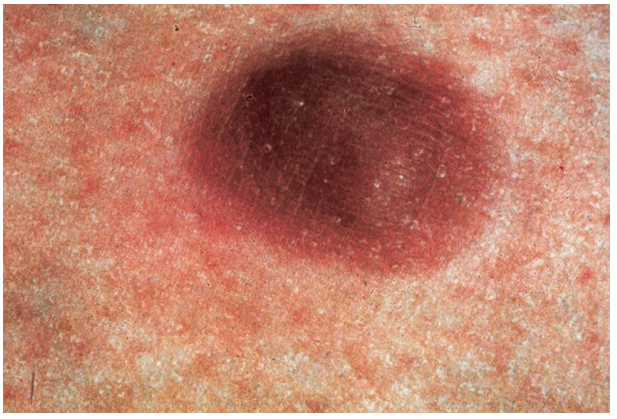

Fig 1. MCC: this 2.0-cm pigmented tumor on the thigh was clinically misdiagnosed as a melanocytic lesion. (By courtesy of Mosby-Wolfe, Times Mirror International Medical Publishers; from: Phillip H. McKee, Pathology of the Skin, ed 2, 1996, reprinted with permission).

Initially, MCC was thought to be a cancer with a good prognosis, as only one out of the first five patients described by Toker[7] succumbed to the disease, and only three deaths occurred in the first 24 reported cases.[27] However, MCC has subsequently been shown to be a highly aggressive and lethal tumor, comparable with small-cell lung cancer and melanoma in its behavior with regards to recurrence, metastatic spread, and mortality. The overall recurrence rate ranges from 55% to 79%, occurring most often locally or in regional lymph nodes,[15,18,22,23,39-41] with the majority of recurrences appearing within the first 6 to 12 months after initial diagnosis.

Pathology

Merkel cell tumor arises in the dermis and frequently extends into the subcutaneous fat. The epidermis is often intact but may be ulcerated and in a minority of cases there is epidermal involvement either as neuroendocrine carcinoma-in-situ or else as single cells randomly distributed throughout the epithelium.[25,42] Squamous cell carcinoma-in-situ may additionally be present in the overlying epidermis.[43]

The tumor is composed of small blue cells with hyperchromatic nuclei and minimal cytoplasm. Mitoses are frequently abundant and apoptosis is often widespread. Lymphovascular invasion is an almost invariable feature.[25] Three main histologic subtypes are recognized: intermediate, small cell, and trabecular (the least common).[44] These have no clinical significance, and in the majority of cases, an admixture is present.[45] The intermediate variant is the most often encountered. It consists of nodules and diffuse sheets of basophilic cells with imperceptible cytoplasm and round or oval vesicular nuclei, the dispersed chromatin giving a pathognomonic watery appearance (Fig 2A). The small-cell variant is histologically identical to other small-cell carcinomas and consists of irregular, hyperchromatic

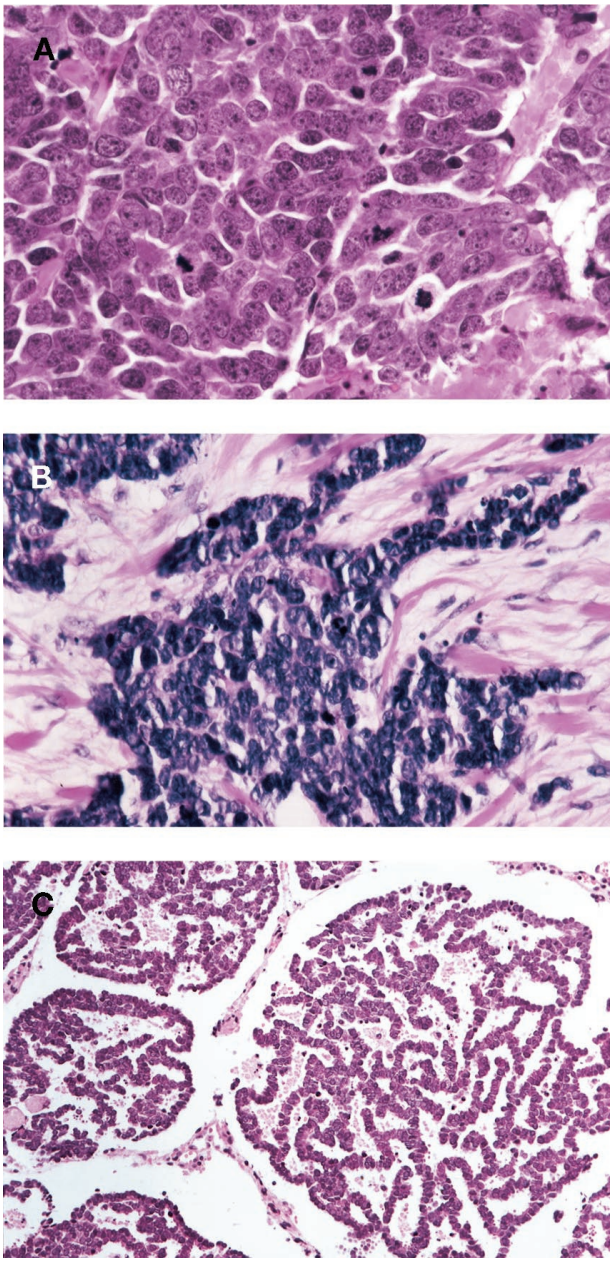

Fig 2. (A) Intermediate variant of MCC showing vesicular, basophilic nuclei with prominent nucleoli and multiple mitoses. (B) Small-cell variant, histologically indistinguishable from bronchial small-cell carcinoma. (C) Trabecular variant is rare and normally only seen as a small component of a mixed variant. (By courtesy of Mosby-Wolfe, Times Mirror International Medical Publishers; from: Phillip H. McKee, Pathology of the Skin, ed 2, 1996, reprinted with permission).

Table 1. Immunocytochemical Differential Diagnosis of Merkel Cell Tumor

Tumor	CK20	CK7	NSE	NFP	S100	LCA	CD99	TTF-1
Merkel cell tumor	+	−	+	+	−	−	Rarely + (cytoplasmic)	−
Small-cell carcinoma of lung	−	+	+	+/−	−	−	Rarely + (cytoplasmic)	+
Lymphoma	−	−	−	−	−	+	−	−
Peripheral primitive neuroectodermal tumor	−	−	+	Rarely +	−	−	+ (membranous)	−
Small-cell melanoma	−	−	+	−	+	−	−	−

Abbreviations: NSE, neuron-specific enolase; NFP, neurofilament protein; LCA, leukocyte common antigen; TTF-1, thyroid transcription factor 1.

cells, often showing crush artifact and frequently displaying nuclear molding (Fig 2B). This variant particularly must be distinguished from metastatic small-cell carcinoma, eg, of bronchial derivation. The trabecular variant consists of delicate ribbons of small basophilic cells typically displaying nuclear molding (Fig 2C). Spindle-cell forms are also encountered, and occasionally keratinization and ductal differentiation is seen.

The diagnosis of Merkel cell tumor and, in particular, its distinction from metastatic small-cell carcinoma is made by the identification of an appropriate immunocytochemical profile (Table 1). The tumor cells express CAM 5.2 and more specifically cytokeratin (CK) 20, often as a paranuclear dot (Fig 3).[46-53] CK7, which identifies bronchial small-cell carcinoma, is typically negative. Similarly, thyroid transcription factor, a homeodomain-containing nuclear transcription factor, is present in small-cell carcinoma of bronchial derivation but is not present in Merkel cell tumor.[54-57] In contrast, neurofilament protein, again presenting as a paranuclear dot, is commonly present in Merkel cell tumor but is often absent in bronchial small-cell carcinoma.[53,58-60]

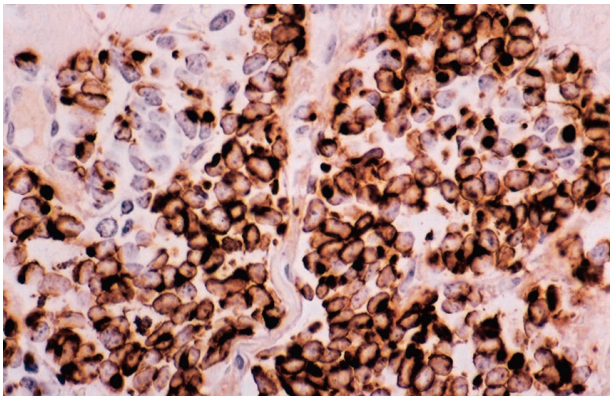

Fig 3. MCC: cytochemical stain demonstrating cytokeratin expression (CK 20) with conspicuous paranuclear dots. (By courtesy of Mosby-Wolfe, Times Mirror International Medical Publishers; from: Phillip H. McKee, Pathology of the Skin, ed 2, 1996, reprinted with permission).

Merkel cell tumor frequently reacts to neuron-specific enolase, synaptophysin and chromogranin, and epithelial membrane antigen and BER-EP4 may also be expressed.[61,62] The tumor cells are invariably negative for S100-protein and leukocyte-common antigen, thereby excluding small-cell melanoma and cutaneous lymphomatous deposits. Electron microscopy discloses electron-dense granules (80 to 200 nm) and paranuclear globular aggregates of keratin and neurofilament protein.

The histologic differential diagnosis of Merkel cell tumor includes peripheral primitive neuroectodermal tumor in addition to metastatic small-cell carcinoma, small-cell melanoma, and cutaneous lymphoma.

Etiology

Little is known about specific etiologic factors in the pathogenesis of MCC. However, it has been linked, much like melanoma, to increased sun exposure, both in its anatomic and geographical distribution. Miller and Rabkin[10] describe a correlation between the solar ultraviolet (UV) B index and regional differences in the incidence of MCC.[10] One study demonstrates a typical UVB-induced *p53* mutation in a case of MCC.[63] A recent report describes a 100-fold increased incidence of MCC in patients treated with methoxsalen and UVA for psoriasis,[64] and infrared light damage has also been described as a risk factor.[65] In addition, several reports describe the appearance of MCC with synchronous or metachronous squamous cell cancer[43,66-70] or basal cell cancer of the skin,[66] either indicating sun exposure as a risk factor for developing MCC or a common precursor cell for both. Arsenic exposure has also been implicated in the pathogenesis.[71]

Another possible cause of MCC is an impaired immune status, either from iatrogenic immunosuppression, human immunodeficiency virus infection, or neoplasia. MCC has been reported to occur after organ transplantation, with 41 cases published from the Cincinnati Tumor Registry.[72] The incidence of MCC in this patient population was 0.9% of all de-novo malignancies after transplantation, with a younger mean age at onset (46 years) than that seen in the general

population. Other studies report MCC after solid organ transplant and in patients on immunosuppressive therapy for rheumatoid arthritis.[10,73-80] A recent report describes the occurrence of MCC 7 years after bone marrow transplant for non-Hodgkin's lymphoma.[81] Two cases of MCC arising in human immunodeficiency virus–infected patients have been reported,[82,83] and another association has been noted between MCC and chronic lymphocytic leukemia.[84-86] These reports suggest that immunosuppression of various causes may play a role in the pathogenesis of MCC, especially in younger patients. An immunologic basis is also discussed to explain the increased frequency of secondary malignancies in patients with MCC (25%) as compared with those with melanoma (5.8%).[70]

Molecular Aspects

A number of chromosomal abnormalities have been described in MCC. The most intriguing one possibly relating to the pathogenesis of this disease is a deletion on the short arm of chromosome 1 (1p36).[87-90] This chromosomal region has also been implicated in the pathogenesis of neuroblastoma[91] and melanoma,[92] suggesting that a tumor suppressor gene may be localized here. *p73* has been localized to 1p36.33;[93] however, a recent study found mutations of the *p73* gene in only one out of 10 patients with MCC,[63] similar to the infrequent mutations of *p73* in melanoma.[94] The tumor suppressor gene *p53* is thought to be transiently expressed in MCC; a mutant *p53* protein has been identified in six of nine patients who had poor clinical outcome as compared with none of 10 patients with a more favorable outcome.[95] Another important abnormality may be the reported loss of heterozygosity in chromosome 3p21,[96] the same region that is also affected in more than 90% of patients with small-cell lung cancer and for which a candidate tumor suppressor gene, Ras association domain family 1 (*RASSF1A*) gene, has recently been postulated.[97,98] This may indicate a common oncogenic pathway for MCC and small-cell lung cancer both of which exhibit neuroendocrine origin and share the histologic feature of small blue cells and the tendency to metastasize early.

Several other chromosomal abnormalities have been described in MCC, including the following: trisomy 1,[99,100] trisomy 6,[100-102] trisomy 11,[99,102] and trisomy 18,[103] and deletion of chromosome 7.[102] One study found two to three copies of chromosome X in 71% of tumor cells compared with only one copy in almost all normal Merkel cells.[103] Loss of heterozygosity has also been reported in chromosome 10q[104] and chromosome 13, where one report shows a frequent deletion of the retinoblastoma gene *RB1*.[99,105,106] Although some of these findings suggest the involvement of tumor suppressor genes or oncogenes in the pathogenesis of MCC, no conclusive candidates have been identified, and too little is known about the prognostic value of the reported abnormalities.

Diagnostic Evaluation

After histologic diagnosis, patients should undergo further imaging studies for staging and to exclude other sites as the primary source of a small-cell carcinoma. Computed tomography (CT) of the chest should be performed to exclude the presence of a lung mass suspicious for small-cell lung cancer as well as evidence of metastatic disease. Abdominal and pelvic CT scans are also useful to assess for metastases.[107] Octreotide scans have been used to detect various neuroendocrine neoplasms, especially in the gastrotintestinal tract, since the early 1990s,[108] and several case reports evaluating this technique in the diagnosis of primary MCC and metastatic disease have reported a greater sensitivity than CT.[109-115] The presence of somatostatin receptors as documented in these scans has also been used therapeutically in MCC and other neuroendocrine tumors.[109,114,116] Positron emission tomography (PET) using fluorodeoxyglucose has become an important diagnostic tool in many cancers. It has been used in the staging of melanoma, especially in the detection of metastatic disease.[117-119] Two reports describe the usefulness of PET in the initial staging and follow-up after chemotherapy in patients with MCC.[120,121]

TREATMENT

Due to the rare occurrence of MCC, no prospective clinical studies assessing initial surgical therapy, radiation therapy, or chemotherapy have been performed. The general treatment approach to MCC according to stage is listed in Table 2.[22]

Surgical Treatment. Surgical excision with tumor-free margins is the primary therapy for stage I disease. Up to two thirds of patients with localized disease at the time of presentation will develop local recurrence or lymph node involvement. Therefore, 2- to 3-cm wide and 2-cm deep margins have been generally recommended.[22,23,26,122] Yiengpruksawan et al[22] detected local recurrence in four out of 27 patients with margins $\leq$ 3 cm, but in none of 11 patients with margins $>$ 3 cm; and O'Connor et al[123] reported a similar reduction in local recurrence when margins of 3 cm were compared were 2 cm. However, more recently, Ott et al[16] reported no difference in survival in 33 patients when resection margins were $>$ or $<$ 2 cm; and Gillenwater et al[124] demonstrated no difference in outcome in 18 patients based on margins $<$ 1 cm, 1 to 2 cm, or $>$ 2 cm.

Mohs micrographic surgery[125] has been proposed as being more successful in controlling local disease than

Table 2. Proposed Staging System for Merkel Cell Carcinoma, Relationship to Overall Survival and Recommended Treatment

Stage		Median Survival (months)	5-Year Survival (%)	Treatment Recommendations
I	Localized disease		64	Surgery: local excision with > 2 cm margin, sentinel lymph node biopsy Radiation therapy: adjuvant treatment after resection with 45-50 Gy Chemotherapy: little experience for adjuvant chemotherapy
IA	≤ 2 cm	30		
IB	> 2 cm	26		
II	Lymph node involvement	18	47	Surgery: local excision with > 2 cm margin, lymph node dissection Radiation therapy: adjuvant therapy to both primary site and lymph node region Chemotherapy: little experience for chemotherapy
III	Distant metastases	5	0	Radiation therapy: palliative use of radiation Chemotherapy: CAV or EP most commonly used

Abbreviations: CAV, cyclophosphamide, doxorubicin, vincristine; EP, etoposide, cisplatin.

traditional wide excision, especially in such cosmetically sensitive anatomic areas as the face. Uncontrolled clinical experience has been promising,[25,126] but definitive clinical studies still have to be conducted.

Sentinel Lymph Node Biopsy. Pathologic involvement of regional lymph nodes is present in 10% to 30% of all patients presenting with MCC who undergo lymph node dissection.[22,23] The detection of lymph node involvement is another important prognostic factor as noted above. Consequently, elective lymph node dissection has been recommended for younger patients with large lesions or tumors arising in the head and neck region.[22,26,127] Elective regional lymphadenectomy or sentinel-node biopsy was first introduced by Cabanas[128] for penile carcinoma in 1977 but has recently been applied predominantly to patients with melanoma[129,130] and breast cancer,[131,132] because sentinel nodes have been shown to reflect the histology of the remaining lymph nodes in the specific lymph node basin in both cancers. Based on the similarity of MCC and melanoma with regard to the early involvement of regional lymph nodes and sequential metastatic spread, several recent reports have shown the emerging role of lymphoscintigraphy and sentinel lymph node biopsy in MCC.[133-140] The published experience so far is limited to a total number of 49 patients reported with short median follow-up times. Currently, little can be concluded about the therapeutic value of lymph node dissection in preventing regional recurrence. It may have a role in the staging of patients with MCC, sparing patients without sentinel lymph node involvement the morbidity of full lymph node dissection.

Radiation Therapy. Because of the aggressive nature of the disease and the high local and regional failure rates after surgery alone, radiation therapy has been used in the adjuvant setting as well as after resection for local recurrence. MCC cell lines have been shown to be radiosensitive in vitro,[141] and the similarities to small-cell lung carcinoma on light microscopy led to the use of radiation therapy early on.[142] Cotlar et al[143] in 1986 reported their own experience of 10 patients and reviewed another 139 reported in the literature and strongly argued for radiation therapy after initial surgery. Subsequently, several studies from Australia,[144,145] the United Kingdom,[142] Israel,[146] France,[147] Germany,[148] and the United States[16,124,149-151] have argued for the benefits of both adjuvant radiation treatment after initial surgery with curative intent as well as after resection for recurrent MCC and palliation. Best locoregional control was achieved with resection followed by radiation, and a higher rate of recurrence was seen in those patients treated with initial surgery alone. However, these nonrandomized retrospective analyses are very heterogenous with regard to tumor size and location as well as radiation techniques, and only two studies[16,145] suggest a survival advantage with adjuvant radiation. The total radiation doses varied from 30 to 70 Gy, in 20 to 25 daily fractions, with 45 to 50 Gy total being most commonly used. Ott et al[16] reported a radiation dose of ≥ 45 Gy as having a significant impact on locoregional control and prolonged survival in nine patients, whereas a subset of seven patients who received less than 45 Gy had a poorer outcome.[16] Because of the limited number of patients with MCC, convincing data from prospective studies are not available, and other reports suggest no significant benefit from adjuvant radiation.[22,29] In addition to radiation therapy, concomitant hyperthermia has been shown to successfully treat a few patients with MCC.[152,153] Given the current experience, adjuvant radiation therapy at 45 to 50 Gy administered to the primary site after surgical resection as well as to involved lymph nodes may be beneficial to prevent local recurrence.

Chemotherapy. Chemotherapy is the least studied therapeutic component of therapy for MCC. Although MCC was initially considered resistant to chemotherapy, subsequent reports have shown good results with chemotherapeu-

Table 3. Chemotherapy Regimen Commonly Used for the Treatment of MCC

Regimen
Cyclophosphamide, doxorubicin, vincristine
Etoposide, cisplatin
Cyclophosphamide, epirubicin, vincristine
Cyclophosphamide, doxorubicin, vincristine alternating with etoposide, cisplatin
Cyclophosphamide, doxorubicin, vincristine + prednisone
Doxorubicin, cisplatin ± bleomycin
Doxorubicin
Doxorubicin/ifosfamide
Cisplatin ± doxorubicin
Mitoxantrone

tic approaches similar to the therapeutic regimens for small-cell lung cancer and neuroendocrine tumors in other locations.[154,155] Over the last 15 years, many different regimens have been used both in the adjuvant setting as well as for recurrent or metastatic disease and as primary therapy in patients with inoperable tumors.[25,146,156-160] The different regimens commonly used in this disease are listed in Table 3. However, because of the low incidence of MCC, no prospective randomized trials have been reported. Although chemotherapy in recurrent or metastatic MCC is frequently used, its value as adjuvant therapy remains to be determined. Another problem is the advanced age of most patients with MCC who may be intolerant to the high doses of chemotherapy some of these regimens require. Most cases of toxicities have been related to bone marrow suppression and neutropenia.[14,161] Tumor lysis syndrome with renal failure has been described after chemotherapy with doxorubicin and ifosfamide in a patient with extensive metastatic MCC.[162] Voog et al[14] recently reviewed the use of chemotherapy in locally advanced or metastatic MCC in 107 patients from 37 reports.[14] Among the chemotherapeutic agents, cyclophosphamide (56%), anthracyclines (49%), and cisplatin (25%) were most commonly used, usually as part of polychemotherapy. The overall objective response rate was 60% and was slightly higher in the setting of locally advanced disease (69%) than in metastatic disease (57%). Regimens combining doxorubicin and cisplatin as well as those containing fluorouracil had significantly higher response rates when compared with other therapies, and those patients who responded with complete remission to initial chemotherapy had a significantly increased rate of survival after 1 and 5 years compared with those with only partial or no responses. However, toxic deaths related to chemotherapy occurred in nine (8.4%) of 107 patients, especially in those patients older than 65 years of age. Tai et al[161] reviewed the outcome of 204 patients with MCC who were treated with chemotherapy, including those managed in the adjuvant as well as metastatic disease settings. In this review, 68% of patients without distant metastases responded to the various treatments with complete remission, partial response, or minor response. The overall response rate for distant metastases was 59%. The combination of cyclophosphamide, doxorubicin, and vincristine, or cyclophosphamide in combination with epirubicin and vincristine ± prednisone, and etoposide plus cisplatin were the most commonly used drug regimens, with an overall combined response rate of 69%. Taxanes, although used in the treatment of small-cell lung cancer, have not been reported in the treatment of MCC.

So far, two cases of MCC treated with high-dose chemotherapy followed by either autologous bone marrow[163] or stem-cell[164] transplantation have been reported; the first achieved a partial remission, whereas the second patient was in complete remission for 6 months before tumor recurrence in the lung. Currently, chemotherapy has no established role in the adjuvant treatment of MCC. For the treatment of metastatic disease, however, cyclophosphamide, doxorubicin, and vincristine and etoposide plus cisplatin are the most commonly used regimens.

Other Therapeutic Agents. Biologic agents, especially interferon[165-168] and tumor necrosis factor,[120,165,169,170] have occasionally been used in the therapy of MCC. Two groups from Japan have reported complete regression of local tumors without recurrence as a result of direct intratumoral injection of tumor necrosis factor.[169,170]

Based on the observation that MCC cell lines require several growth stimuli to survive in culture[171] and one of them may be nerve growth factor, farnesylthiosalicylic acid, an inhibitor of ras signal transduction, has been studied and shown to inhibit the growth of human MCC in severe combined immunodeficiency (SCID) mice.[172] Based on the report that *bcl-2* is frequently overexpressed in MCC cells compared with normal Merkel cells,[171,173,174] *bcl-2* antisense oligonucleotides have been used in SCID mice with MCC; inhibition of human MCC tumor growth has been observed when compared with controls or cisplatin-treated animals.[175] These preliminary studies give hope for new treatment approaches in the future based on identifiable molecular targets.

DISCUSSION

MCC is a rare skin cancer of likely neuroendocrine origin with approximately 470 new cases in the United States annually, affecting mainly whites, and likely related to sun exposure and immunosuppressed states. It is an aggressive tumor, and survival is dependent on stage and localization at presentation. Histologically, MCC is a small blue cell

tumor, and differentiation from small-cell lung cancer and the small-cell variant of melanoma is achieved by immunohistochemistry, using S100, CK20, CK7, and thyroid transcription factor-1. Although several genetic abnormalities have been reported, no strong pathogenetic correlation has been identified. The diagnostic evaluation includes CT imaging; octreotide and PET scans may be helpful in diagnosis and staging. Wide surgical excision is the primary mode of treatment for nonmetastatic disease, and sentinel lymph node biopsy may aid in the staging. Adjuvant radiation therapy at 45 to 50 Gy to the primary site and involved lymph nodes can prevent local recurrences and may improve survival. Chemotherapy, based on regimens for small-cell lung cancer, leads to tumor regression in up to 70% of cases with metastatic disease but has no established role in the adjuvant setting.

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