Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features

Michelle Heath, MD,[a] Natalia Jaimes, MD,[a] Bianca Lemos, MD,[a] Arash Mostaghimi, MD,[d] Linda C. Wang, MD, JD,[d] Pablo F. Peñas, MD, PhD,[e] and Paul Nghiem, MD, PhD[a,b,c]
Seattle, Washington; Boston, Massachusetts; and Sydney, Australia

Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a mortality of 33%. Advanced disease at diagnosis is a poor prognostic factor, suggesting that earlier detection may improve outcome. No systematic analysis has been published to define the clinical features that are characteristic of MCC.

Objective: We sought to define the clinical characteristics present at diagnosis to identify features that may aid clinicians in recognizing MCC.

Methods: We conducted a cohort study of 195 patients given the diagnosis of MCC between 1980 and 2007. Data were collected prospectively in the majority of cases, and medical records were reviewed.

Results: An important finding was that 88% of MCCs were asymptomatic (nontender) despite rapid growth in the prior 3 months (63% of lesions) and being red or pink (56%). A majority of MCC lesions (56%) were presumed at biopsy to be benign, with a cyst/acneiform lesion being the single most common diagnosis (32%) given. The median delay from lesion appearance to biopsy was 3 months (range 1-54 months), and median tumor diameter was 1.8 cm. Similar to earlier studies, 81% of primary MCCs occurred on ultraviolet-exposed sites, and our cohort was elderly (90% >50 years), predominantly white (98%), and often profoundly immune suppressed (7.8%). An additional novel finding was that chronic lymphocytic leukemia was more than 30-fold overrepresented among patients with MCC.

Limitations: The study was limited to patients seen at a tertiary care center. Complete clinical data could not be obtained on all patients. This study could not assess the specificity of the clinical characteristics of MCC.

Conclusions: To our knowledge, this study is the first to define clinical features that may serve as clues in the diagnosis of MCC. The most significant features can be summarized in an acronym: AEIOU (*a*symptomatic/lack of tenderness, *e*xpanding rapidly, *i*mmune suppression, *o*lder than 50 years, and *u*ltraviolet-exposed site on a person with fair skin). In our series, 89% of primary MCCs had 3 or more of these findings. Although MCC is uncommon, when present in combination, these features may indicate a concerning process that would warrant biopsy. In particular, a lesion that is red and expanding rapidly yet asymptomatic should be of concern. (J Am Acad Dermatol 2008;58:375-81.)

Merkel cell carcinoma (MCC) is a highly aggressive skin cancer with a mortality of approximately 33% at 3 years,[1] higher than that of melanoma (approximately 15%). Data from Surveillance, Epidemiology, and End Results (SEER)[2] show a 3-fold increase in MCC from 0.15 to 0.44 per

From the University of Washington Division of Dermatology[a]; Seattle Cancer Care Alliance[b]; Fred Hutchinson Cancer Research Center, Seattle[c]; Dana Farber/Brigham and Women's Cancer Center, Boston[d]; and Westmead Hospital, University of Sydney.[e]

Dr Jaimes is currently affiliated with Dermatology, Universidad Pontificia Bolivariana, Medellín, Colombia. Dr Mostaghimi is currently affiliated with Beth Israel Deaconess Medical Center, Boston, Mass.

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Reprint requests: Paul Nghiem, MD, PhD, University of Washington, 815 Mercer St, Seattle, WA 98109. E-mail: pnghiem@u.washington.edu.

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Abbreviations used:

AEIOU: asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than 50 years, ultraviolet-exposed/fair skin
CLL: chronic lymphocytic leukemia
MCC: Merkel cell carcinoma
SEER: Surveillance, Epidemiology, and End Results
UV: ultraviolet

100,000 annually from the years 1986 to 2001. This trend is continuing,[3,4] and approximately 1000 to 1500 new cases will be diagnosed in the United States in 2007. Several factors likely contribute to this including an aging population, increased aggregate sun exposure, and a higher number of individuals who are immune suppressed. Furthermore, the advent of the immunohistochemical marker cytokeratin-20 improved recognition of this disease. In the era before widespread cytokeratin-20 immunohistochemistry, laborious electron microscopy was required to make an accurate MCC diagnosis. Indeed, 66% of MCC cases in one series from this era would have been misdiagnosed (as metastatic small cell lung cancer, basal cell carcinoma, lymphoma, or other metastatic carcinoma) if electron microscopy had not been performed demonstrating the characteristic neurosecretory granules within cytoplasmic extensions.[5]

Management of MCC is controversial. To date there have been no controlled therapeutic trials in this disease. In most cases, surgical excision with sentinel lymph node biopsy[1,6] followed by radiation[7,8] is indicated. Conventional adjuvant chemotherapy lacks evidence of survival benefit and may in fact be associated with poorer outcomes.[1,9] A consensus treatment algorithm has been developed by the National Comprehensive Cancer Network.[10]

MCC prognosis is highly associated with the extent of disease at presentation. Disease-specific survival for local disease is greater than 90%, decreasing to 52% with nodal involvement.[3] If distant metastatic disease is present, expected survival is typically less than 10% at 3 years.[1] As delay in diagnosis could allow disease progression, early detection and clinician recognition of this disease may improve survival. Currently, a detailed description of the clinical characteristics of MCC at the time of diagnosis has not been published. Specifically, a PubMed search of "Merkel cell carcinoma clinical features" (performed on October 24, 2007) yielded 87 studies, none of which described the clinician's presumptive diagnosis, the color or symptomatic nature of the lesion, or the time to biopsy after lesion appearance.

The purpose of this study was to identify key clinical features that may assist the clinician in recognizing this aggressive skin cancer at an earlier and potentially more curable point.

METHODS

Institutional review board approval was obtained from each institution. Tumor registry data and prospective patient identification (beginning in 2003) were used to identify 195 patients from 3 medical centers in Boston, Mass (Dana Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital) and two medical centers in Seattle, Wash (Seattle Cancer Care Alliance and University of Washington Medical Center). The study included patients with a pathologic diagnosis of MCC between 1980 and 2007.

Patient characteristics, clinical features of the lesion (ie, site, tenderness, color, growing time, and diameter), stage at presentation, interval from appearance to biopsy, and the clinician's impression at the time of biopsy were reviewed. The initial clinical impression was that recorded by the physician in either the clinical notes or on the pathology requisition. Presumptive diagnoses were listed in 106 patients. Of these, 78 had a single diagnosis whereas 28 had multiple clinical impressions reported; each of the 141 impressions was considered independently. The clinical impressions were stratified into benign, malignant, and indeterminate lesions.

Estimation of age-adjusted chronic lymphocytic leukemia (CLL) prevalence in the United States was determined for the age groups 50 to 69 years and greater than or equal to 70 years using the SEER[11] database (2004 data; 30,465 and 51,579 cases, respectively) and dividing this by the US Census Bureau[12] 2004 population estimate for those age groups (60,489,662 and 26,653,288 persons, respectively). For patients with solid organ transplantation prevalence, a specific query was submitted to United Network for Organ Sharing,[13] which provided data regarding all living recipients of solid organ transplantation engrafted between October 1, 1986, and June 30, 2006, who had not reported graft failure (223,307 cases). This total number was divided by the 2006 US Census Bureau's[12] estimated total US population (299,398,484 persons).

RESULTS

Patient characteristics

As shown in Table I, the median age at diagnosis was 69 years, with 90% of patients being older than 50 years. There was a slight male predominance with a ratio of 1.4:1 (58.5% male and 41.5% female). The

vast majority of patients were white (98%), with only 4 patients being nonwhite (3 Asian and 1 black). Profound immunosuppression including HIV (3 patients), CLL (8 patients), or solid organ transplantation (4 patients) was noted in 7.8% of patients. The mean age of presentation of the patients who were immunosuppressed in this series was comparable with that of the immunocompetent group; 65 versus 67 years, respectively.

In all, 106 patients (57%) presented with local disease. Seventy patients (37%) presented with nodal disease; of these, 27 (14% of the total patients) had nodal presentation with no identified primary. Eleven patients (6%) presented with metastatic disease. Information regarding the time from lesion appearance to biopsy was available in 144 patients with a primary lesion. The median time to biopsy was 3 months (mean 5.3 months, range 1-54 months).

Table I. Patient characteristics at diagnosis

	No.	Percentage
Age, y (median 69, range 34-97)		
<50	20	10.3
50-70	92	47.1
>70	83	42.6
Sex		
Male	114	58.5
Female	81	41.5
Race		
White	191	97.9
Black	1	0.5
Asian	3	1.5
Immunosuppression (n = 193)		
HIV	3	1.6
Solid organ transplantation	4	2.1
Chronic lymphocytic leukemia	8	4.1
Total	15	7.8*
Extent of disease (n = 187)		
Local only (<2 cm diameter)	68	36.4
Local only (≥2 cm diameter)	38	20.3
Nodal	70	37.4†
Distant metastatic	11	5.9
Interval from appearance to biopsy (n = 144)		
Median: 3 mo		
Mean: 5.3 mo		
Range: 1-54 mo		

N = 195 except when otherwise noted.
*A 16-fold overrepresentation of immunosuppression as compared with general US population based on estimated prevalences of: chronic lymphocytic leukemia 0.029%, HIV 0.4%, and living recipients of solid organ transplantation with viable grafts 0.075%.
†Nodal disease assessed by palpation or histologic evaluation (when performed).

Tumor characteristics

Examples of MCC presentation that include lesions initially thought to be a cyst or other benign process are shown in Fig 1. As outlined in Table II, the diameter of the primary tumor was less than 1 cm in 32 patients (21.3%), 1 to 2 cm in 65 patients (43.3%), and greater than 2 cm in 53 patients (35.3%). The median tumor size was 1.8 cm (n = 146 patients with primary tumor size data). The most common color of the primary lesion was red/pink, seen in 56% of patients, followed by blue/violaceous noted in 26%. Most (88%) of the lesions were asymptomatic. In all, 63% of patients reported rapid growth of their tumor within 3 months. Only a minority (11%) reported no changes in the size of their primary lesion.

Fig 2 shows the distribution of primary MCC tumors and those that presented in the lymph node without a known primary. Most lesions appeared on sun-exposed skin; however, 19% presented on the buttock or other minimally sun-exposed areas. The most common anatomic site of the primary lesion was the head and neck (29%), followed by the lower limbs (24%) and upper extremities (21%). Nodal disease in the setting of no identified primary tumor was diagnosed in 27 patients (14%) (Table III).

Among the group of 106 patients for whom a presumed clinical diagnosis was reported, the majority (56%) of clinical impressions were benign (Table IV). A cyst or acneiform lesion was the single most common presumptive diagnosis (32%), followed by lipoma (6%), dermatofibroma or fibroma (4%), and vascular lesion (4%). Malignant diagnoses comprised an additional 36% of the clinical impressions, with nonmelanoma skin cancer being the most common of these (19%), followed by lymphoma (6%), metastatic carcinoma (2%), and sarcoma (2%). The correct clinical diagnosis of MCC was made presumptively in only two cases (1%).

The 5 most common clinical features were used to create an acronym: AEIOU (*a*symptomatic/lack of tenderness, *e*xpanding rapidly [≤3 months], *i*mmunosuppression, *o*lder than 50 years, and location on an *u*ltraviolet [UV]-exposed site) (Table V). All 5 of these data points were known in 62 patients. In all, 89% of patients met 3 or more criteria, 52% met 4 or more criteria, and 7% met all 5 criteria.

DISCUSSION

This study of 195 patients was conducted to identify key features of MCC that may aid clinicians in recognizing when a biopsy may be warranted. The basic demographic profile of our cohort is similar to that described in other studies: mostly elderly, white, and with a slight male predominance.

The anatomic distribution of the tumors seen in our study further supports sun exposure as a risk

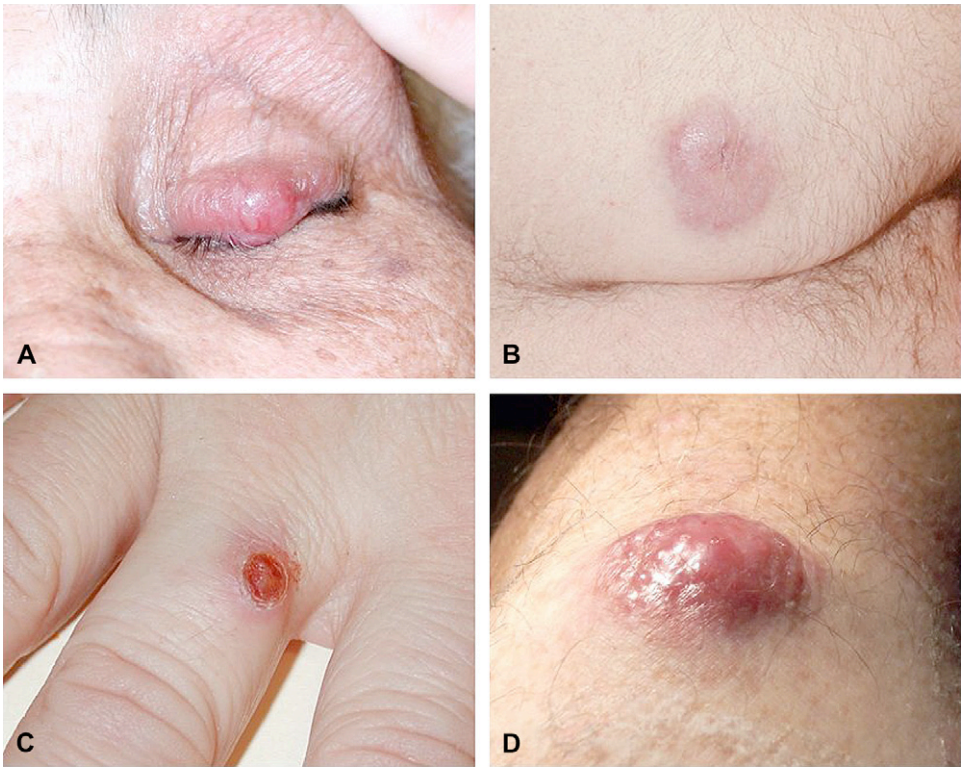

Fig 1. Clinical examples of Merkel cell carcinoma (MCC). **A**, Eyelid lesion thought to be rapidly growing chalazion. **B**, Nontender MCC that arose on buttock of patient with HIV. MCC diagnosis was markedly delayed because of history of multiple epidermoid cysts. **C**, Finger lesion that was clinically suggestive of pyogenic granuloma or amelanotic melanoma. **D**, MCC that arose on sun-exposed area of arm in man with fair skin. (Photograph courtesy of http://www.merkelcell.co.uk, used with permission.)

Table II. Merkel cell carcinoma primary tumor characteristics

	No.	Percentage
Size (N = 150)		
<1 cm	32	21.3
1-2 cm	65	43.3
>2 cm	53	35.3
Color (N = 81)		
Red/pink	45	55.6
Blue/violaceous	21	25.9
Skin colored	13	16.0
Yellowish/white	2	2.5
Asymptomatic (N = 89)		
Yes	78	87.6
No	11	12.4
Expansion rate (n = 91)		
Rapid (≤3 mo)	57	62.6
Slowly (>3 mo)	24	25.4
No changes noted	10	11.0

factor for the development of MCC, consistent with prior studies. Agelli and Clegg[3] used SEER registry data to demonstrate a positive association between geographic UVB radiation indices and age-adjusted MCC incidence among white patients in a variety of US cities. In patients receiving psoralen plus UVA for psoriasis, Lunder and Stern[14] reported the incidence of MCC to be approximately 100 times that expected in the general population. In our series, 81% of cases presented on UV-exposed skin. Although sun exposure is strongly associated with MCC, as in melanoma, MCC can arise in the absence of significant UV exposure. Of importance, 5% of patients had tumors on highly sun-protected sites (buttock or vulva), and 14% had tumors arise on partially protected sites (abdomen, thighs, and hair-bearing scalp).

Profound immunosuppression also appears to be an important risk factor for MCC. Indeed, 7.8% of our patients had some form of immunosuppression, including HIV, CLL, or iatrogenic suppression secondary to solid organ transplantation. This frequency is a 16-fold overrepresentation of that expected in the general US population, in which the estimated prevalences are 0.4% for HIV,[15] 0.029% for CLL,[11,12] and 0.075% for solid organ transplantation.[12,13]

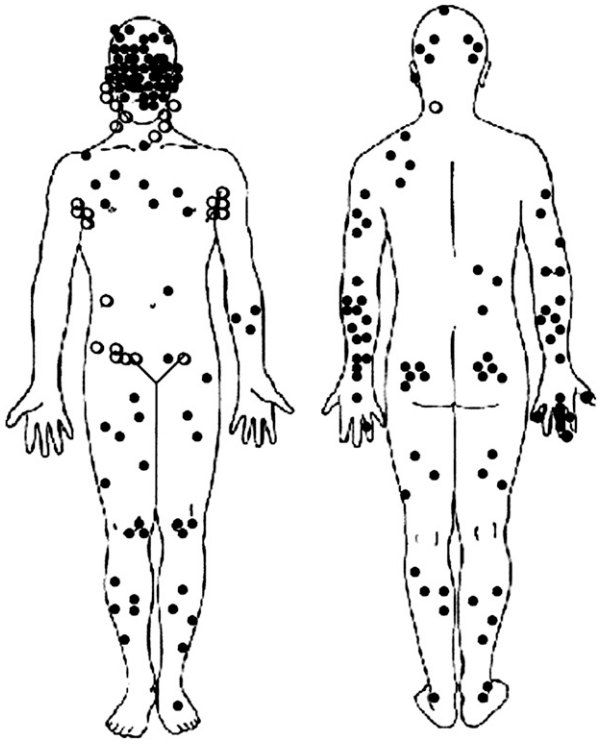

Fig 2. Distribution of Merkel cell carcinoma at presentation in 195 patients. Primary skin lesion (*solid circle*) was seen in 168 patients (86%). In all, 27 (14%) presented with nodal involvement and no known primary (*open circles*).

Table III. Presenting anatomic location

	No.	Percentage
Primary skin lesion	168	86
Head and neck	56	29
Lower limb	46	24
Upper limb	40	21
Trunk	16	8
Buttock	9	5
Vulva	1	0.5
No known primary (nodal presentation)	27	14

Table IV. Clinician's impression of primary lesion at time of biopsy

Clinical diagnosis	No.	Percentage
Benign	79	56
Cyst/acneiform lesion	45	32
Lipoma	9	6
Dermatofibroma/fibroma	6	4
Vascular	5	4
Insect bite	4	3
Other*	10	7
Malignant	51	36
Nonmelanoma skin cancer	27	19
Lymphoma	9	6
Metastatic carcinoma	3	2
Sarcoma	3	2
MCC	2	1
Other*	7	5
Indeterminate	11	8
Nodule/mass	8	6
Other*	3	2

In all, 21 patients had two presumed diagnoses listed, 2 had 6, and one had 4: each was included independently.
Clinical impression listed in 106 patients with a total of 141 independent presumed diagnoses.
MCC, Merkel cell carcinoma.
*Benign: pyogenic granuloma, eccrine spiradenoma, scar, neurofibroma, Sweet's syndrome, inflammatory, benign lesion; malignant: melanoma, dermatofibrosarcoma protuberans, atypical fibroxanthoma, aplastic lesion; indeterminate: appendageal tumor, neural tumor, lymphocytic infiltrate.

Table V. AEIOU features of Merkel cell carcinoma

AEIOU parameter	No.	Percentage
Asymptomatic	78/89	88
Expanding rapidly	57/91	63
Immune suppressed	15/193	7.8‡
Age > 50 y	175/195	90
UV exposed	136/168	81
Fair skin	191/195	98
Criteria met by MCC primary lesions*		
≥3	55	89
≥4	20	32
5	4	7

AEIOU, Asymptomatic/lack of tenderness, expanding rapidly, immune suppression, older than 50 years, ultraviolet-exposed/fair skin; *MCC*, Merkel cell carcinoma; *UV*, ultraviolet.
*N = 62 for which all 5 criteria are known.
‡A 16-fold overrepresentation of immunosuppression.

An association of MCC with HIV and solid organ transplantation is documented in the literature. Miller and Rabkin[16] reported a roughly 10-fold increase in MCC after solid organ transplantation, and Engels et al[17] found a 13-fold increase among patients who were HIV positive. Further highlighting the importance of immune function in MCC, Friedlaender et al[18] described regression of MCC metastases after discontinuation of cyclosporine in a patient with kidney transplantation.

Among our patients who were immunosuppressed, CLL was particularly overrepresented (4.1%). The age-adjusted incidence of CLL in our cohort was 2.4% for those aged 50 to 69 years and 6.5% for those aged 70 years or older, representing a respective 48-fold and 34-fold increase above that expected in the US population for those age groups. MCC arising in the setting of CLL has been

described,[19-23] but, to our knowledge, this is the first quantitation of the degree to which MCC is overrepresented in this disease. We acknowledge the potential for referral bias in our series because patients who are immune suppressed may be more likely to be seen in tertiary medical centers. However, in 3 of the 15 cases, MCC was diagnosed first, and the immune-suppressed state (HIV or CLL) was discovered as part of the MCC workup. This finding also supports the need for practitioners to consider further workup for immunosuppression in patients presenting with MCC.

In agreement with an earlier study of patients with transplantation, we observed more advanced disease at time of presentation in the immunosuppressed group; 10 of the 15 patients (67%) who were immunocompromised presented with either nodal or distant metastatic disease as compared with 42% in the immunocompetent group (difference not statistically significant). In contrast to reports of organ transplant recipients and patients who are HIV positive developing MCC at an earlier age,[17,24,25] we did not find a difference in the mean ages of immunosuppressed and immunocompetent patients with MCC. This likely reflects the inclusion of 8 patients with CLL, a disease with a mean age of 65 years.

Clinicians thought most lesions were benign before biopsy, which may have contributed to a delay in the diagnosis. Although not quantified, many of our patients reported they had been reassured by a physician about the benign nature of their lesion. Indeed, several of the characteristic MCC features were present at that earlier visit. It is hoped that publicizing the clinical characteristics of MCC may result in an earlier diagnosis in some cases.

We identified several tumor characteristics that may aid a clinician in suspecting MCC, summarized as AEIOU (Table V). Of particular note, we consider lack of tenderness an important feature in MCC as many other lesions that are rapidly growing and red or pink (such as an inflamed cyst, the most common presumed diagnosis) would likely be tender.

Here we describe the first systematic analysis of the clinical features of MCC. We have identified several characteristics that in combination are highly sensitive for the diagnosis of MCC. Although we do not have data to address the specificity of these features, it is likely to be low given the rarity of MCC. Among lesions encountered in routine clinical practice that display multiples of these features, only a few may be MCC whereas others, such as squamous cell carcinoma or keratoacanthoma, would also have required a biopsy. Thus, the use of these criteria to aid in the decision to perform a biopsy may be appropriate. Given the correlation between survival and stage at presentation,[1] identifying patients at an earlier and potentially more curable point is highly desirable for MCC.

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