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

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Abstract

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—To define the clinical characteristics present at diagnosis in order to identify features that may aid clinicians in recognizing MCC.

Methods—Cohort study of 195 patients diagnosed with 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 to be benign, with a cyst/acneiform lesion being the single most common diagnosis (32%) given at biopsy. 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 prior studies, 81% of primary MCCs occurred on UV-exposed sites, and our cohort was elderly (90% over age 50), predominantly Caucasian (98%), and often profoundly immune suppressed (7.8%). An additional novel finding was that chronic lymphocytic leukemia was more than 30-fold over-represented among MCC patients.

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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—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** - Asymptomatic/lack of tenderness, **E**xpanding rapidly, **I**mmune suppression, **O**lder than age 50, and **U**V-exposed site on a person with fair skin. In our series, 89% of primary MCCs had three 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.

Introduction

Merkel cell carcinoma (MCC) is a highly aggressive skin cancer with a mortality of approximately 33% at 3 years¹, higher than that of melanoma (approximately 15%). Data from Surveillance, Epidemiology, and End Results (SEER) show a three-fold increase in MCC from 0.15 to 0.44 per 100,000 annually from the years 1986 to 2001². This trend is continuing, and approximately 1000–1500 new cases will be diagnosed in the United States in 2007^{3, 4}. Several factors likely contribute to this including an aging population, increased aggregate sun exposure and a higher number of immune suppressed individuals. Furthermore, the advent of the immunohistochemical marker cytokeratin-20 (CK-20) improved recognition of this disease. In the era before widespread CK-20 immunohistochemistry, laborious electron microscopy was required to make an accurate MCC diagnosis. Indeed, 66% of MCC cases in one series 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 Network¹⁰.

MCC prognosis is highly associated with the extent of disease at presentation. Disease-specific survival rates for local disease are greater than 90%, falling to 52% with nodal involvement³. If distant metastatic disease is present, expected survival is typically less than 10% at three years¹. As delay in diagnosis could allow disease progression, early detection and clinician recognition of this disease may improve survival rates. At present, 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 10/24/07) 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 is to identify key clinical features that may assist the clinician in recognizing this aggressive skin cancer at an earlier and potentially more curable point.

Patients and 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 (Dana Farber Cancer Institute, Brigham and Women’s

Hospital, Massachusetts General Hospital) and 2 medical centers in Seattle (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 (i.e. site, tenderness, color, growing time, 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 while 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 US was determined for the 50–69 and ≥ 70 year old age groups using the SEER¹¹ database (2004 data; 30,465, and 51,579 cases, respectively) and dividing this by the US Census Bureau¹² 2004 population estimate for those age groups (60,489,662, and 26,653,288 persons, respectively). For solid organ transplant patient prevalence, a specific query was submitted to UNOS¹³ (United Network for Organ Sharing) which provided data regarding all living solid organ transplant recipients engrafted between 10/1/1986 and 6/30/2006 who have not had a reported graft failure (223,307 cases). This total number was divided by the 2006 US Census Bureau's¹² 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 over age 50. There was a slight male predominance with a ratio of 1.4:1 (58.5% males and 41.5% females). The vast majority of patients were Caucasian (98%), with only 4 patients being non-white (3 Asian and 1 Black). Profound immunosuppression including HIV (3 patients), CLL (8 patients) or solid organ transplant (4 patients) was noted in 7.8% of patients. The mean age of presentation of the immunosuppressed patients in this series was comparable to that of the immunocompetent group, 65 vs. 67 years respectively.

One hundred and six 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).

Tumor characteristics

Examples of MCC presentation which include lesions that initially were thought to be a cyst or other benign process are shown in Figure I. As outlined in Table II, the diameter of the primary tumor was <1 cm in 32 patients (21.3%), 1–2 cm in 65 patients (43.3%) and >2 cm in 53 patients (35.3%). 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. Sixty-three percent 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.

Figure II shows the distribution of primary MCC tumors as well as 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 non-melanoma 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 five 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 age 50, and location on a **U**V-exposed site (Table V)). All five of these data points were known in 62 patients. Eighty-nine percent 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, Caucasian and with a slight male predominance.

The anatomic distribution of the tumors seen in our study further supports sun-exposure as a risk factor for the development of MCC, consistent with prior studies. Agelli *et al.* used SEER Registry data to demonstrate a positive association between geographic UV-B radiation indices and age-adjusted MCC incidence among White patients in a variety of US cities³. In patients receiving PUVA (psoralen + UV-A) for psoriasis, Lunder and Stern reported the incidence of MCC to be approximately 100 times that expected in the general population¹⁴. In our series, 81% of cases presented on UV-exposed skin. While sun exposure is strongly associated with MCC, as in melanoma, MCC can arise in the absence of significant UV exposure. Importantly, 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 over-representation of that expected in the general US population, in which the estimated prevalences are 0.4% for HIV¹⁵, 0.029% for CLL^{11, 12}, and 0.075%^{12, 13} for solid organ transplantation.

An association of MCC with HIV and solid organ transplantation is documented in the literature. Miller *et al.* reported a roughly ten-fold increase in MCC after solid organ transplantation¹⁶, and Engels found a 13-fold increase among HIV-positive patients¹⁷. Further highlighting the importance of immune function in MCC, Friedlaender *et al.* described regression of MCC metastases after discontinuation of cyclosporine in a kidney transplant patient¹⁸.

Among our immunosuppressed patients, CLL was particularly over-represented (4.1%). The age-adjusted incidence of CLL in our cohort was 2.4% for 50–69 year olds and 6.5% for ≤ 70 year olds, 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 the best of our knowledge, this is the first quantitation of the degree to which MCC is over-represented in this disease. We acknowledge the potential for referral bias in our series because immune suppressed patients 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 a prior study of transplant patients, we observed more advanced disease at time of presentation in the immunosuppressed group; ten of the fifteen (67%) immunocompromised patients presented with either nodal or distant metastatic disease as compared to 42% in the immunocompetent group (difference not statistically significant). In contrast to reports of organ transplant recipients and HIV positive patients developing MCC at an earlier age^{17, 24, 25}, we did not find a difference in the mean ages of immunosuppressed and immunocompetent MCC patients. This likely reflects the inclusion of 8 patients with CLL, a disease with a mean age of 65.

Clinicians thought most lesions were benign prior to 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 Merkel cell carcinoma. We have identified several characteristics that in combination are highly sensitive for the diagnosis of MCC. While 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 multiple of these features, only a few may be MCC while 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 presentation¹, identifying patients at an earlier and potentially more curable point is highly desirable for Merkel cell carcinoma.

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Abbreviations

CLL	chronic lymphocytic leukemia
HIV	Human Immunodeficiency Virus
MCC	Merkel cell carcinoma

Acronym

AEIOU

Asymptomatic/lack of tenderness, Expanding rapidly, Immune suppression, Older than age 50, UV-exposed/fair skin

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Figure I. Clinical examples of MCC

A. An eyelid lesion that was thought to be a rapidly growing chalazion.

B. A non-tender MCC that arose on the buttock of a patient with HIV. The MCC diagnosis was markedly delayed because of a history of multiple prior epidermoid cysts.

C. A finger lesion that was clinically suggestive of a pyogenic granuloma or amelanotic melanoma.

D. A MCC that arose on a sun-exposed area of the arm in a man with fair skin (photo courtesy of <http://www.merkelcell.co.uk>, used with permission).

Figure II. Distribution of MCC at Presentation in 195 Patients

A primary skin lesion (solid circle ●) was seen in 168 patients (86%). Twenty-seven (14%) presented with nodal involvement and no known primary (open circles ○).

Table I**Patient Characteristics at Diagnosis**

	No.	Percentage
Age (yrs) (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 transplant	4	2.1%
Chronic lymphocytic leukemia	8	4.1%
TOTAL	15	7.8% [‡]
Extent of Disease (n=187)		
Local only (< 2cm diameter)	68	36.4%
Local only (≥ 2cm diameter)	38	20.3%
Nodal	70	37.4% ^T
Distant Metastatic	11	5.9%
Interval from Appearance to Biopsy (n=144)		
Median: 3 months		
Mean: 5.3 months		
Range: 1–54 months		

N=195 except when otherwise noted.

[‡] 16-fold over-representation of immunosuppression as compared to the general US population based on estimated prevalences of: chronic lymphocytic leukemia 0.029%, HIV 0.4% and living solid organ transplant recipients with viable grafts 0.075%

^T Nodal disease assessed by palpation or histologic evaluation (when performed).

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 months)	57	62.6%
Slowly (> 3 months)	24	25.4%
No changes noted	10	11.0%

Table III

Presenting Anatomic Location

	No.	Percentage
Primary Skin Lesion	168	85%
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 the 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%
Non-Melanoma 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%

[‡]Clinical impression listed in 106 patients with a total of 141 independent presumed diagnoses.

* 21 patients had 2 presumed diagnoses listed, 6 had 6, and 1 had 4: each was included independently.

Other⁺

Benign: Pyogenic granuloma, eccrine spiradenoma, scar, neurofibroma, sweets syndrome, "inflammatory", "benign lesion"

Malignant: melanoma, dermatofibrosarcoma protuberans, atypical fibroxanthoma, "aplastic lesion"

Indeterminate: appendageal tumor, neural tumor, lymphocytic infiltrate

Table V**AEIOU Features of MCC**

AEIOU Parameter	No.	Percentage
Asymptomatic	78/79	88%
Expanding Rapidly	57/91	63%
Immune Suppressed	15/193	7.8% [‡]
Older than Age 50	157/195	90%
UV exposed	136/168	81%
Fair Skin	191/165	98%
Criteria Met by MCC		
Primary Lesions [*]		
≥ 3 criteria	55	89%
≥ 4 criteria	20	32%
5 criteria	4	7%

[‡] 16-fold over-representation of immunosuppression

^{*} N=62 for which all five criteria are known