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Evaluation of clinical characteristics and pre-biopsy impressions of primary Merkel cell carcinoma of the skin

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Abstract

Merkel cell carcinoma is an aggressive carcinoma of the skin notable for protean presentation on physical examination. A retrospective cohort of 232 patients with primary cutaneous Merkel cell carcinoma was reviewed for availability of data on pre-biopsy clinical differential diagnosis based on clinical examination. Data was available for 192 patients (83%). The three most common impressions were cyst (33.3%), basal cell carcinoma (31.8%), and squamous cell carcinoma (19.8%). Merkel cell carcinoma was correctly suspected in only 13 cases (6.8%). A greater proportion of lesions that were less than or equal to two cm in diameter (10.2%) or carried BCC as a co-diagnosis (11.5%) were correctly suspected as Merkel cell carcinoma prior to biopsy, versus lesions greater than two cm in diameter (1.6%) or carrying SCC as a co-diagnosis (2.6%), suggesting that clinicians may be anchoring on the well-publicized concept of Merkel cell carcinoma as a small, pearly papule in real-world practice.

Keywords: diagnosis, Merkel cell carcinoma, staging

Introduction

Compounding a great propensity for metastasis and an increasing incidence, Merkel cell carcinoma (MCC) typically presents with primary cutaneous tumors that vary widely in appearance and are prone to misdiagnosis, even by experienced dermatologists [1,2]. Despite improved awareness in the last decade, in part due to successful immunotherapy development programs and the Merkel Cell Carcinoma Multi-Center Interest Group [3], we find that MCC continues to be rarely included in the clinical differential prior to biopsy. We discuss here several observed trends in clinical diagnosis and propose a subset of primary tumors that may be especially prone to escaping clinical suspicion as MCC.

Methods

This study was approved by the Massachusetts General Hospital, IRB Protocol# 2019P002459. A cohort of 232 patients diagnosed with primary MCC between 2016 and 2019 available from the Mass General Brigham medical record was reviewed for availability of data on pre-biopsy clinical impressions of primary cutaneous MCC tumors within pathology reports and clinician notes. Data on patient and disease characteristics and pre-biopsy differential

Abbreviations

BCC	Basal cell carcinoma
MCC	Merkel cell carcinoma
NMSC	Non-melanoma skin cancer
NOS	not otherwise specified
NUB	Neoplasm of uncertain behavior/neoplasm not otherwise specified
SCC	Squamous cell carcinoma
UV	Ultraviolet radiation

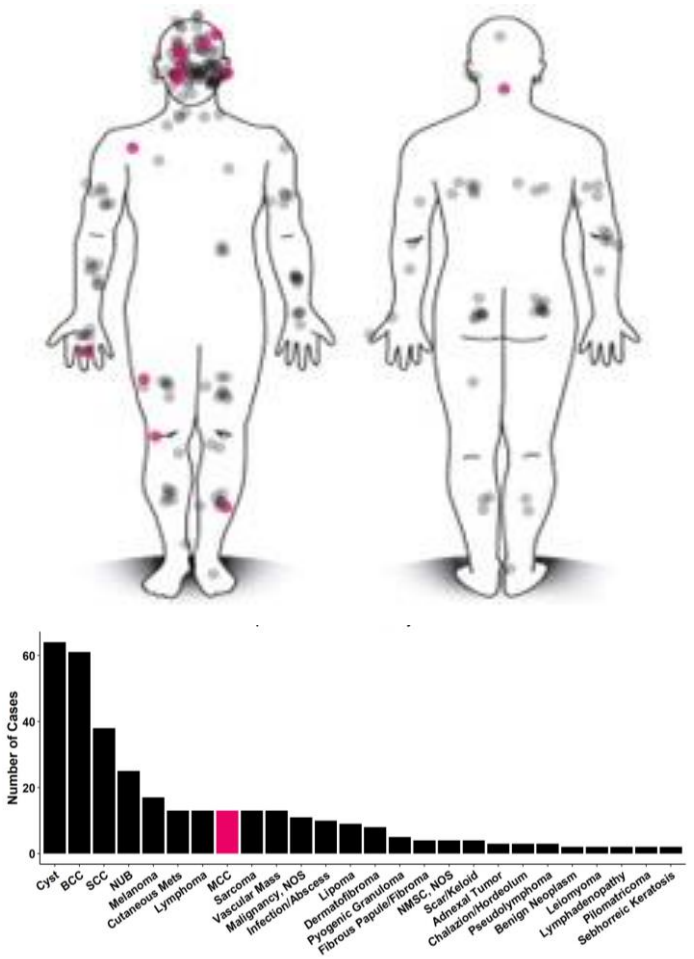

Figure 1. *Anatomic distribution and pre-biopsy clinical impressions of primary Merkel cell carcinoma (MCC) tumors.* ***A)*** *Anatomic distribution of primary cutaneous MCC tumors, restricted to cases for which pathology report was available to confirm location of primary tumor (N=228). Lesions correctly suspected as MCC prior to biopsy are represented in red (N=13/228).* ***B)*** *Histogram illustrating number of cases of primary cutaneous MCC in which the listed pre-biopsy clinical impressions were made (N=192).*

BCC, basal cell carcinoma; MCC, Merkel cell carcinoma; NOS, not otherwise specified; NUB, neoplasm of uncertain behavior/neoplasm not otherwise specified.

diagnosis was collected and stored on the REDCap platform [4]. Data visualizations were created in R.

Results

59.5% of the cohort were male (N=138/232), 78.0% (N=181) were over 65 years old, and 96.6% (N=224) were white. The majority of primary cutaneous tumors were located on the head, neck, or extremities (86.6%), (Table 1; **Figure 1A**). A total of 61.7% of tumors were less than or equal to two 2 cm in diameter on clinical examination (Table 1). 83% of cases (192/232) had at least one pre-biopsy clinical impression available within the clinician note or clinical history section of the pathology report (Table 1). The top three impressions were cyst (33.3%, or 64/192 cases), basal cell carcinoma (BCC; 31.8%), and squamous cell carcinoma (SCC; 19.8%), (**Figure 1B**). Merkel cell carcinoma was included in the differential diagnosis in only 13 cases (6.8%), comparable to Heath et al.'s observed rate of two out of 106 (1.9%) in their 2008 review (**Table 2**), [5]. The majority of correctly diagnosed tumors were less than or equal to 2cm in diameter on examination (11/12) and located on the head or neck (8/13). Correct diagnoses were primarily made by dermatologists (11/13 cases) practicing in either academic or community settings. In the 192 cases with pre-biopsy differential diagnosis available, no primary care provider ever correctly suspected MCC, stressing the continued need to raise awareness of the disease in this essential provider group.

Discussion

We highlight two suggestive trends from our retrospective review, acknowledging that any trend likely reflects a combination of phenotypic variability in MCC primary lesions as well as unaccounted biases in clinician diagnoses. First, only one of 63 lesions over 2cm in size with impressions available (1.6%) was correctly suspected as MCC, versus 11 of 108 tumors with diameters less than or equal to two 2 cm (10.2%), (**Table 2**). Second, only one one of 38 cases with SCC featured in the differential diagnosis (2.6%) also included MCC, a case in which BCC was notably also listed in the differential diagnosis (**Table 2**). In contrast, including the latter case, 7 of 61 BCC-resembling lesions (11.5%) were correctly suspected as MCC. Together, these observations suggest that larger lesions or lesions conventionally "squamous cell" in appearance, likely with hyperkeratosis or scale, may be less likely to draw clinical suspicion for MCC. Owing to the retrospective nature of this study,

comprehensive data on clinical appearance of primary lesions at presentation was not available. Although our ability to draw conclusions is consequently limited and confounders may exist, we suspect that our observations reflect clinician expectation of a primary MCC tumor as being a smooth, small or intermediately sized, erythematous papule on the head and neck in real-world practice. This is commensurate, for instance, with how the Skin Cancer Foundation describes the average Merkel cell carcinoma primary lesion on detection [6].

Interestingly, the proportion of SCC-resembling primary tumors, as evidenced by inclusion of SCC in the differential diagnosis (38/192, or 19.8%), was similar to the reported frequency of tumors that display a "combined" histology in the literature. In 2018, Carter et al. found that <20% of MCC featured both neuroendocrine and other carcinomatous or sarcomatous, most often squamous, histology; strikingly, all were Merkel cell polyoma virus-negative [7]. Given that 92% of SCC-resembling tumors (35/38) were located on sun-exposed regions

Table 2. *Cases with Merkel cell carcinoma included in clinical differential diagnosis prior to biopsy.*

No.	Non-MCC clinical impression(s) prior to biopsy	Primary tumor size on exam (cm)	Location of primary tumor	Clinical stage, AJCC 8th Ed.	Provider setting[a]	Provider specialty
1	Adnexal tumor, cyst, melanoma	[b]	Lower extremity	IIA	Community	Surgery
2	BCC, chondroid syringoma, melanoma, metastatic cancer, pilomatricoma	1.5	Head/neck	I	Academic	Dermatology
3	BCC	1	Head/neck	III	Community	Dermatology
4	BCC, cyst	1.8	Head/neck	I	Community	Dermatology
5	Cyst, metastatic cancer	1	Chest	III	Academic	Dermatology
6	BCC, fibrous papule, hemangioma, melanoma	0.5	Head/neck	I	Academic	Dermatology
7	BCC	1	Head/neck	IIB	Community	Surgery
8	Lymphoma	2-3	Head/neck	III	Community	Dermatology
9	Melanoma	0.8	Head/neck	I	Community	Dermatology
10	BCC, NUB, SCC	1.4	Lower extremity	I	Community	Dermatology
11	Benign neoplasm, cyst	2	Lower extremity	I	Community	Dermatology
12	BCC, melanoma	1.5	Head/neck	III	Community	Dermatology
13	Adnexal tumor, metastatic cancer, NUB	1	Upper extremity	I	Community	Dermatology

Non-MCC impressions, tumor features, staging, and provider setting in which diagnosis was made for cases in which Merkel cell carcinoma was correctly suspected prior to biopsy. BCC, basal cell carcinoma; MCC, Merkel cell carcinoma; NUB, neoplasm of uncertain behavior/neoplasm not otherwise specified; SCC, squamous cell carcinoma.

[a]Location of practice of provider who originally included MCC in the clinical differential diagnosis prior to biopsy.

[b]Clinical dimensions of tumor not available. Greatest dimension on pathology was 1.5cm.

of the head, neck, and extremities, we hypothesize that the contrasting macroscopic phenotypes of "scale versus no scale" may be associated with the dichotomous pathogenesis of virus-negative/ultraviolet-driven MCC versus virus-positive MCC, respectively. Our data on polyomavirus immunohistochemistry and seropositivity for this retrospective cohort is incomplete. The proposed association is therefore speculative and merits further inquiry with follow-up studies utilizing tissue profiling data. In any case, raising awareness specifically for this posited less frequent phenotype of primary tumor may improve clinical diagnosis rates of MCC by dermatologic and non-dermatologic providers.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Patient characteristics and pre-biopsy clinical impressions in cases of primary cutaneous Merkel cell carcinoma.*

	No.	%
Age (yrs) (Median 74.5, Range 37-99)		
<50	2	0.9
50-70	80	34.5
>70	150	64.7
Sex		
Male	138	59.5
Female	94	40.5
Immunosuppression		
HIV	1	0.4
Solid organ transplant[a]	1	0.4
Hematologic malignancy/disorder[b]	27	11.6
Medical immunosuppression[c]	16	6.9
TOTAL	45	19.4
Anatomic location of primary cutaneous tumors (N=232)		
Head/neck	102	44.0%
Upper extremity	54	23.3%
Lower extremity	45	19.4%
Trunk	16	6.9%
Buttocks	15	6.5%
Size of primary cutaneous tumors on physical exam (N=193)		
<=2cm	119	61.7%
>2cm, <=5cm	66	34.2%
>5cm	8	4.1%
Clinical impressions of primary cutaneous tumors prior to biopsy (N=192)		
Cyst	64	33.3%
Basal cell carcinoma	61	31.8%
Squamous cell carcinoma	38	19.8%
NUB/neoplasm, NOS	25	13.0%
Melanoma	17	8.9%
Cutaneous metastases	13	6.8%
Lymphoma	13	6.8%
Merkel cell carcinoma	13	6.8%
Sarcoma	13	6.8%
Vascular tumor or malformation	13	6.8%
Malignancy, NOS	11	5.7%
Infection/abscess	10	5.2%
Lipoma	9	4.7%
Dermatofibroma	8	4.2%
Pyogenic granuloma	5	2.6%
Fibrous papule/fibroma	4	2.1%
Non-melanoma skin cancer, NOS	4	2.1%
Scar/keloid	4	2.1%
Adnexal tumor	3	1.6%
Chalazion/hordeolum	3	1.6%
Pseudolymphoma	3	1.6%
Benign neoplasm	2	1.0%
Leiomyoma	2	1.0%
Lymphadenopathy	2	1.0%
Pilomatricoma	2	1.0%
Seborrheic keratosis	2	1.0%
Other[d]	22	11.5%

Patient characteristics and distribution of anatomic location, tumor size on physical exam, and clinical impressions for a 5-year cohort of patients diagnosed with primary cutaneous Merkel Cell Carcinoma. NOS, Not Otherwise Specified.

[a] Renal transplant ~8.5 years prior to diagnosis of Merkel cell carcinoma.

[b] Cases with history of at least one of the following hematologic malignancies/disorders prior to Merkel cell carcinoma diagnosis: acute myeloid leukemia, cutaneous B-cell lymphoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, cutaneous T-cell lymphoma, diffuse large B-cell lymphoma, Hodgkin lymphoma, marginal zone lymphoma, myelodysplastic syndrome, monoclonal gammopathy of undetermined significance, multiple myeloma, or non-Hodgkin lymphoma, not otherwise specified.
[c] Patient who did not receive transplant or have history of hematologic malignancy/disorder but were medically immunosuppressed for inflammatory bowel disease or dermatologic, rheumatologic, or other auto-inflammatory indication at time of Merkel cell carcinoma diagnosis.
[d] 22 cases had at least 1 impression in the "Other" category. These were: actinic keratosis, atypia, chondroid syringoma, congenital mass, epithelioma, erythema multiforme, foreign body, giant cell tumor, glomus tumor, granuloma annulare, granuloma faciale, inflammatory mass, leukemia cutis, mass, necrotizing lobular panniculitis with vasculitis, nerve sheath tumor, neurofibroma, nevus, nodular fasciitis, panniculitis, rheumatoid nodule, rosacea, ruptured follicle, soft tissue tumor, superficial thrombophlebitis, tendon sheath tumor, tophus, traumatic fat necrosis.