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A better prognosis for Merkel cell carcinoma of unknown primary origin

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Abstract

BACKGROUND: There is limited evidence that Merkel cell carcinoma (MCC) arising from a nodal basin without evidence of a primary cutaneous (PC) site has better prognosis. We present our experience at 2 tertiary care referral centers with stage III MCC with and without a PC site.

METHODS: Fifty stage III MCC patients were identified between 1996 and 2011. Clinical data were analyzed, with primary endpoints being disease-free survival and overall survival.

RESULTS: Of stage III patients, 34 patients presented with a PC site and 16 patients with an unknown primary (UP) site. Treatment strategies varied; of patients with UP vs PC sites, 25% vs 44% underwent combined regional lymphadenectomy and radiation, with an additional 25% vs 15% receiving chemotherapy. The median disease-free survival for a UP site was not reached vs 15 months for a PC site (hazards ratio = .48, $P = .18$). The median overall survival for a UP site was not reached vs 21 months for a PC site (hazards ratio = .34, $P = .03$). Multivariate analysis showed that UP status was a significant factor in overall survival ($P = .002$).

CONCLUSIONS: Stage III MCC with a UP site portends a better prognosis than MCC with a PC site.

Merkel cell carcinoma (MCC) is an uncommon cutaneous malignancy associated with a poor prognosis that has had an increasing incidence both nationally and worldwide over the past decade.[1–3] US Surveillance, Epidemiology and End Results data have indicated at least a 3-fold increase in incidence to .44 cases per 100,000 from 1986 to 2001.[3] Although presentation is variable, it most typically appears in older, white men between the 6th and 8th decade of life and in patients with a history of sun exposure.[4–8] MCC is differentiated from other cutaneous malignancies by its characteristic histopathologic appearance. It is an undifferentiated small-cell malignancy, with both neuroendocrine and epithelial features, often described as having scant cytoplasm and multiple nucleoli within vesicular nuclei.[6,9,10] However, it can be difficult to definitively distinguish MCC from other undifferentiated neoplastic entities

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such as small-cell carcinoma of the lung, metastatic neuroendocrine tumors, lymphoma, and amelanotic melanoma. Immunohistochemistry is mandatory to assist with differentiating pathology; MCC will consistently show reactivity for cytokeratin 20, neuron-specific enolase, neurofilament protein, and BCL-2 but not TTF-1, S-100, CD3, or CD20.[7,11–16]

The challenges in the diagnosis and treatment of MCC are amplified when it presents as an isolated metastasis within a lymph node. Nodal involvement in MCC constitutes stage III disease. American Joint Committee on Cancer staging further divides stage III into IIIA and IIIB when node positivity is microscopic (ie, identification by sentinel node) or clinically palpable.[17] Thus, MCC with an unknown primary (UP) site by definition is stage IIIB. MCC with a UP site has been sporadically described in the literature as case reports. In a literature review of 875 cases, Akhtar et al[18] reported an overall incidence of 5% for MCC of a UP site; institutional incidence has been reported as high as 19%.[19] Interestingly, when only stage IIIB MCC is considered, UP disease comprises 40% of cases.[20,21] There are 2 recent reports that suggest that stage III MCC of a UP site has a better prognosis compared with stage III MCC with a known primary cutaneous (PC) site. In 1 Australian case series of 91 stage IIIB MCC patients, a 70% reduced risk of dying from MCC with a UP vs a PC site was shown, with a 69% reduced risk of relapse.[20] Similarly, in an American single-institution analysis of 500 patients with MCC of all stages, patients with stage IIIB MCC of a UP had a 5-year cumulative incidence of death of 43% compared with 67% for stage IIIB MCC with a known PC site.[21] However, descriptions of MCC of a UP are by and large sporadic case reports. We present to describe our experience with MCC of a UP site with treatment strategies and outcomes compared with stage III MCC.

Methods

Under institutional review board approval, we identified 50 patients with stage III MCC from 2 tertiary care referral centers treated between the years 1996 and 2011. Data regarding demographics, tumor stage, surgical and chemoradiation treatment, and clinicopathologic outcomes were collected and analyzed. Additional data regarding dates of death were obtained from the National Social Security Death Index. Pathology for each tumor was reviewed and restaged in accordance to the American Joint Commission on Cancer TNM staging classification for MCC (7th edition).[22]

In our study, both the disease-free survival (DFS) rate and the overall survival (OS) rate were calculated from the date of diagnosis (either the date of excisional biopsy or needle biopsy). We chose the date of diagnosis for uniformity because not all patients underwent subsequent definitive surgery. Baseline demographics and disease characteristic were summarized and compared using the Student *t* test or the chi-square test depending on whether the variable under consideration was continuous or categoric. For OS and DFS, the Kaplan-Meier curves were constructed and compared using the log-rank test. The univariate Cox proportional hazard model was used to determine the hazard ratio (HR). Multivariate analyses were performed using the Cox model with all variables that could potentially impact survivals included. All analyses were performed using Stata 12.1 (StataCorp, College Station, TX).

Results

Fifty patients with stage III MCC were identified between 1996 and 2011. These included patients who were treated primarily at our institutions and also patients who were treated at outside institutions and referred for a second opinion. Thirty-four patients had a known PC lesion, and 16 patients were found to have lymph node involvement with a UP site. The follow-up time ranged from 1 month to 9 years, with a median follow-up time of 13 months for PC patients and 17 months for UP patients. Sex and median age were similar between the 2 groups, with 70% of all patients being male with a median age of 75 years (Table 1). With respect to patients with PC lesions, the location of the primary lesion was primarily in the extremities, with 26% in a lower extremity and 24% in an upper extremity. The primary lesion was found in the head and neck in 29%, and in the remaining patients, it was found on the trunk. The distribution of nodal disease reflected the distribution of the PC lesion, with 70% in the axillary or inguinal nodes and 32% in the cervical nodes (1 patient had nodal spread to both the cervical and axillary

Table 1 Characteristics of PC vs UP patients

	PC	UP	*P* value
Number of patients	34	16	
Male (%)	24 (71)	11 (69)	.89
Median age	76 (range 38–99)	67 (range 35–86)	.12
Personal history of other cutaneous malignancy (%)	13 (38)	4 (27)	.45
Location of primary (%)		NA	
Head and neck	10 (29)		
Upper extremity	8 (24)		
Lower extremity	9 (26)		
Trunk	6 (18)		
Buttock	1 (3)		
Lymph node basin (%)			
Cervical	11 (32)*	8 (50)	.23
Axilla	14 (41)*	2 (13)	.05
Inguinal	10 (29)	6 (38)	.53

NA = not applicable; PC = primary cutaneous; UP = unkown primary.

*One patient with PC MCC with lymph node spread to both cervical and axillary nodes.

Table 2 Pathologic characteristics

	PC	UP
T staging (%)*		
T1	12 (35)	NA
T2	10 (29)	NA
T3	4 (12)	NA
N staging (%)		
1A	15 (44)	0 (0)
1B	18 (53)	16 (100)
2	1 (3)	0 (0)
TNM stage (%)		
Stage IIIA	15 (44)	0 (0)
Stage IIIB	19 (56)	16 (100)
Nodal dissection		
Total number nodes, median	16 (range 5–35)	21 (range 13–46)
Total positive nodes, median	3 (range 1–16)	1 (range 1–21)
Additional positive nodes other than sentinel node	42%	NA

NA = not applicable; PC = primary cutaneous; UP = unknown primary.
*Eight patients with unknown T staging.

nodes). In contrast, almost half the patients with a UP lesion presented with cervical nodes (47%); 40% presented in the inguinal nodes and only 13% in the axillary nodes (Table 1).

The T stage of PC patients was primarily T1 and T2 (35% and 29%, respectively); 12% were T3 (Table 2). T staging was unable to be determined in 8 patients. The N stage was nearly split between 1A and 1B in PC patients, with 1 patient having in-transit disease (N2). All UP patients by definition had N1B disease. As such, 44% of PC patients had stage IIIA disease and 56% had stage IIIB disease, whereas 100% of UP patients were stage IIIB.

With regards to treatment, patients in both groups were managed with a variety of approaches using a combination of surgery, radiation, and/or chemotherapy (Table 3). All patients with a PC site underwent wide local excision (WLE) of the primary lesion. Thirty of 34 PC patients (88%) also underwent additional regional lymphadenectomy either for clinically positive nodes (n = 18) or after positive sentinel lymph node biopsy (n = 12). Three of the remaining 4 PC patients underwent radiation to the lymph node basin as primary nodal therapy, and the remaining patient received chemotherapy. In comparison, only 50% (8/16) of UP patients underwent regional lymphadenectomy for clinically positive nodes. Four of the remaining 8 patients received radiation (±chemotherapy) to the nodal basin as primary therapy, 2 received chemotherapy alone, and additional nodal therapy was unknown in 2 patients. Overall, 59% of PC patients underwent at least a combined regional lymphadenectomy and radiation approach to positive nodal basins compared with 50% of UP patients. The median total radiation dose was 4,800 cGy for PC patients and 5,940 for UP patients.

In our study, the median DFS for patients with a known PC site was 15 months and was not reached in patients with a UP site (HR = .48; 95% confidence interval [CI], .16 to 1.42; $P = .18$) (Fig. 1A). The fact that the median DFS was not reached for UP patients and the lack of significance reflect inadequate follow-up. Eighteen (53%) PC patients and 4 (25%) UP patients had documented recurrences or progressive disease. Of the PC patients, 10 (56%) had locoregional recurrence, and 9 (50%) had distant metastasis

Table 3 Treatment strategies of PC vs UP patients

	PC	UP
Total patients (n)	34	16
Surgery (%)		
WLE primary cutaneous site	34 (100)	NA
SLN Bx + node dissection	12 (35)	NA
Node dissection	18 (53)	8 (50)
No regional lymphadenectomy	4 (12)	8 (50)
Radiation		
Received radiation to nodal basin (%)	23 (68)	12 (75)
Did not receive radiation (%)	11 (32)	2 (13)*
Median radiation dose	4,800 cGy (range 720–6,000 cGy)	5,940 cGy (range 4,500–6,500 cGy)
Chemotherapy (%)		
Received chemotherapy (carboplatin/etoposide)	8 (24)	8 (50)†
Multimodality therapy (%)‡		
Node dissection + radiation only	15 (44)	4 (25)
Node dissection + radiation + chemo	5 (15)	4 (25)
Node dissection + chemo only	2 (16)	0 (0)
Radiation + chemo only	0 (0)	2 (13)

Bx = biopsy; NA = not applicable; PC = primary cutaneous; UP = unknown primary; WLE = wide local excision.
*Two UP patients, unknown radiation status.
†One UP patient, unknown chemotherapy status.
‡Two UP patients and 1 PC patient with incomplete data.

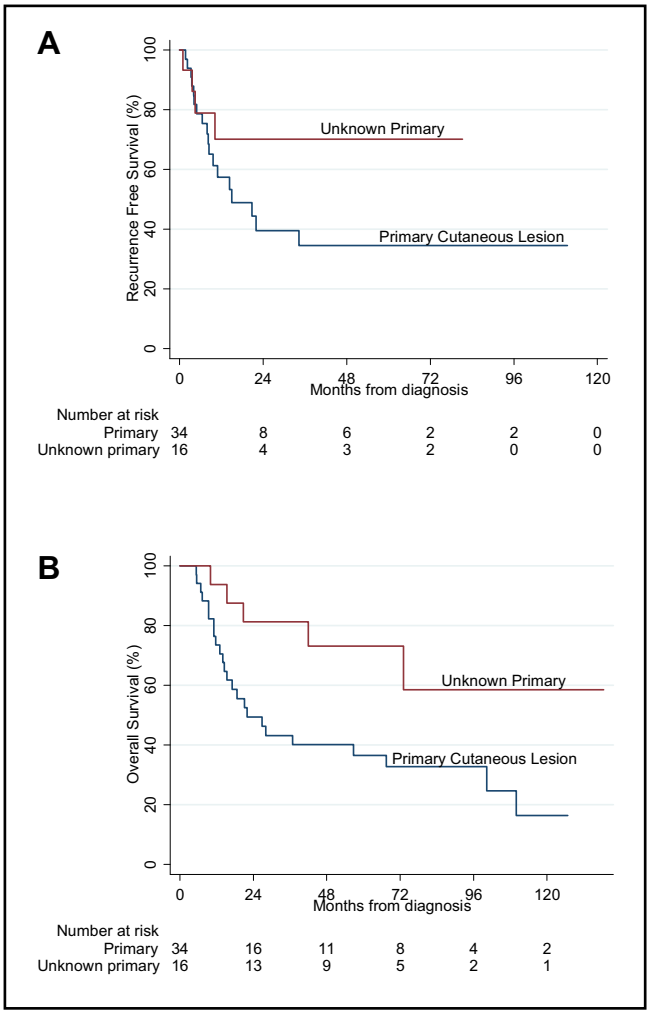

Figure 1 (A) DFS of stage III MCC patients with PC and UP sites by Kaplan-Meier estimation. (B) OS of stage III MCC patients with PC and UP sites by Kaplan-Meier estimation.

(1 patient had both). Of the UP patients, 1 patient had progression of disease, 2 (50%) had locoregional recurrence, and 1 (25%) had distant metastasis.

With regards to OS, the median OS for PC patients was 21 months and was not reached for UP patients (HR = .34; 95% CI, .13 to .89; P = .027) (Fig. 1B). Because survival times were not dependent on follow-up times, we were able to show significantly improved OS for UP patients.

We next considered whether differences in treatment modalities accounted for the discrepancies in DFS and OS between UP and PC patients. Multivariate analysis was performed using age, sex, PC location, number of positive nodes, UP status, lymphadenectomy, chemotherapy treatment, and radiation treatment as variables. When controlling for these variables, a UP status was found to be significant for improved OS (HR = .06; 95% CI, .01 to .34; P = .002). When multivariate analysis was performed for DFS, the use of radiation therapy (HR = .03; 95% CI, .0 to .22; P = .001) and UP status (HR = .1; 95% CI, .01 to .92; P = .04) were related to improved DFS.

Comments

Nodal metastases with a UP site have been described in many types of cancers, including breast, neuroendocrine tumors, and melanoma.[23–25] Cancers with an occult primary lesion present a diagnostic dilemma, and in as many as 30% of these patients, a primary site is never found, even on the postmortem examination. Fortunately, pathologic features and Immunohistochemistry (IHC) on biopsy can often provide clues as to what the primary tumor might be and can direct further therapy. In the case of MCC, diagnosis is suggested by neuroendocrine features on pathology, and differentiation from small-cell lung cancer is made by negative thyroid transcription factor (TTF) staining.

In our study, 32% of our stage III MCC patients were identified as having a UP site; if only stage IIIB patients are considered, then MCC with a UP site accounts for 46% of this group. This initially appeared to be a large proportion but is consistent with other published reports of stage IIIB MCC patients. In a study of 91 stage IIIB patients, Foote et al[20] noted a 40% incidence of UP patients. In another study of 500 patients with all stages of MCC, Fields et al[21] identified 63 patients with a UP site and a total of 115 patients with stage IIIB disease (a 55% incidence).[21]

Although radiation therapy (either as primary treatment or as adjuvant therapy after lymphadenectomy) has been shown to increase DFS in a meta-analysis of 669 patients,[26] 32% of PC patients and 25% of UP patients in our study did not receive radiation treatment although reasons for this are unclear. In general, it is our current practice to perform regional lymphadenectomy for stage III disease, followed by adjuvant radiation (50 to 54 Gy) for disease. If patients decline regional lymphadenectomy, then therapeutic doses (60 to 66 Gy) are administered to nodal basins. In our study, radiation was a significant factor in improved DFS but not OS, which is consistent with the prior meta-analysis.

It is unclear how MCC arises as isolated nodal metastasis without a primary site. However, this phenomenon has been reported and well documented in melanoma.[27–29] Two observations have led to different theories as to how nodal metastases occur in melanomas with a UP site. The first observation is that both primary and metastatic melanomas have been known to undergo spontaneous regression.[30–33] Thus, nodal metastases without a primary site may represent a melanoma that metastasized to the nodal basin and regressed spontaneously at the primary site. The second observation is that neval cells have been identified in lymph nodes; it is postulated that melanoma can arise de novo in lymph nodes.[34,35]

With MCC, spontaneous regression of disease has also been documented in a handful of case reports.[36–40] Regression often occurs after a needle biopsy and is conjectured to be secondary to an immune response precipitated by biopsy.[36,37,40] In some reports, tumor-infiltrating lymphocytes have been shown.[37,41] If this is indeed the mechanism of how isolated nodal metastases develop in MCC without a PC site, a more robust immune response may partially

explain why outcomes are improved in this group. Recent investigations have shown an association with a novel Merkel cell polyomavirus with MCC tumors although the relationship between MCC, immunosuppression, polyoma infection, and regression is not clearly delineated.[42,43] In general, the regression of MCC in case reports has been limited to either stage 1 disease or the involvement of a single metastatic node.[36] In our series, the median number of positive nodes involved in UP patients was 1 although there was a range of up to 21 involved nodes (Table 2). The degree of node positivity did not affect OS in our multivariate analysis, which may reflect a systemic mechanism of why patients with UP lesions have better outcomes.

The primary limitation of our study is the retrospective nature of review. Many of the patients were referred to our centers after receiving treatment at outside institutions, and, as such, many patient records were not complete and unobtainable. As such, it was not always clear why certain patients did not undergo nodal lymphadenectomy or did not receive radiation. Despite this, 38% of PC patients reached 5-year OS, which is comparable with other published series of stage III MCC patients.[20,21] The median OS in a recent review of MCC with a UP origin over a similar time span was noted to be 104 months,[44] and we expect that with further follow-up our median OS for these patients will be similar or improved.

Another limitation was the short median follow-up time. Because of this, information regarding disease recurrence was limited. Thus, when Kaplan-Meier curves were constructed, although a separation in DFS with UP vs PC patients was observed, we could not show significance.

Limitations notwithstanding, our results do support previously published data regarding improved OS survival in MCC patients with a UP site. It has been suggested that UP status may impact future staging systems for MCC,[19,20] and our data would support different survival curves for stage IIIB patients with UP vs PC disease. Ultimately, a prospective evaluation of MCC patients with a UP site would more definitively address this matter. Further research is also warranted to evaluate underlying genetic permutations of these 2 entities to help elucidate improved treatments in the future.

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