Unknown primary Merkel cell carcinoma in the immunosuppressed patient: Case series

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Key words: cutaneous neuroendocrine carcinoma; cutaneous oncology; immunosuppression; MCC; MCC-UP; MCPyV; MCV; merkel cell carcinoma; merkel cell polyomavirus; metastatic merkel cell carcinoma with unknown primary tumor; neuroendocrine carcinoma; oncology; polyomavirus; PyV.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine carcinoma characterized by an increasing incidence.[1] MCC is most commonly found in the setting of advanced age or immunosuppression, and its pathogenesis is closely linked to viral integration of the Merkel cell polyomavirus (MCPyV) into the host genome or DNA mutations due to ultraviolet radiation (UV).[1]

Classically, MCC presents as a rapidly growing red or violaceous skin nodule with the most common site of the first metastasis being regional lymph nodes. However, 5%-25% of patients present with metastatic nodal disease without a primary tumor, known as metastatic MCC with unknown primary tumor (MCC-UP) (Table I).[1-3] Patients with MCC-UP have a better prognosis compared with patients presenting with nodal disease and a known primary tumor (MCC-KP).[3-5] An endogenous antitumor immune response causing regression of the cutaneous lesion and containment of the metastatic disease has been proposed to explain the occult primary and improved outcomes.[5,6] However, the pathogenesis of MCC-UP remains unclear, partially due to the unknown cellular origins of MCC.[1,6]

Here, we report 2 cases of MCC-UP occurring in immunosuppressed patients. The clinical entity is rare, and the ability of MCC-UP to develop in the immunosuppressed/partially immunosuppressed state provides a new insight into the biology of MCC.

Abbreviations used:

MCC:	Merkel cell carcinoma
MCC-KP:	MCC with known primary tumor
MCC-UP:	MCC with unknown primary tumor
MCPyV:	Merkel cell polyomavirus
UV:	ultraviolet radiation

CASE REPORT

Case 1

A 47-year-old Caucasian man with immunosuppression due to lung transplantation secondary to cystic fibrosis presented with a 2-month history of neck adenopathy. Biopsy result was positive for high-grade neuroendocrine carcinoma. Tumor cells were positive for cytokeratin 20 (CK20) and negative for thyroid transcription factor 1 (TTF-1), consistent with MCC. No cutaneous MCC was identified. Staging was negative for distant disease. Neck dissection revealed 13/45 lymph nodes positive for MCC. Extracapsular extension was absent. Immunohistochemistry demonstrated minimal CD8+ infiltrating lymphocytes and no expression of MCPyV T-antigen. Adjuvant radiation therapy was performed.

The patient developed multiple locoregional recurrences beginning 3 months after diagnosis, involving bilateral parotids, neck, and axillae. These were managed with surgery and/or radiation. At 3 years post diagnosis, he is currently undergoing radiotherapy for locally recurrent and progressive disease, without evidence of distant disease.

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;8:19-22.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.11.017

Table I. Patient populations described in this article

Acronym	Population	Description
MCC-KP	MCC with metastasis to regional lymph nodes and/or distant sites* with a known primary tumor	AJCC† stage III or IV disease with T1-T4 primary tumor
MCC-UP	MCC with metastasis to regional lymph nodes and/or distant sites with an unknown primary tumor	AJCC stage IIIA or IV disease with T0 primary tumor (no evidence of primary tumor)
MCC-UP in the setting of immunosuppression	MCC with metastasis to regional lymph nodes and/or distant sites with unknown primary tumor occurring in an immunosuppressed patient	AJCC stage IIIA or IV disease with T0 primary tumor occurring in patients with iatrogenic (organ transplant) or acquired (HIV) immunosuppression

MCC, Merkel cell carcinoma; *MCC-KP*, MCC with known primary tumor; *MCC-UP*, MCC with unknown primary tumor.
*Distant sites include distant skin, distant subcutaneous tissue, distant lymph node(s), and/or viscera.
†American Joint Committee on Cancer (AJCC) TNM Staging Classification for Merkel Cell Carcinoma (8th ed., 2017).

Case 2

A 48-year-old Caucasian man with immunosuppression due to a kidney transplant secondary to polycystic kidney disease presented with right groin adenopathy. Biopsy demonstrated metastatic high-grade neuroendocrine carcinoma. Tumor cells expressed CK20 and neuroendocrine markers and lacked TTF-1, consistent with MCC. No cutaneous MCC was identified. Staging identified liver metastases, which were confirmed by biopsy. CD8+ infiltrating lymphocytes were absent, and the MCPyV T-antigen was not identified in the metastatic lesion. Mutation profiling of 227 cancer genes identified 21 somatic mutations affecting genes, such as *RB1*, *NOTCH1*, and *PTEN*, with no detected *TP53* mutation. Low-level chromosomal copy gain of *MDM4* was also detected. The patient was treated with carboplatin, etoposide, and pembrolizumab. Two months later he developed brain metastases, which were treated with stereotactic radiosurgery. Pembrolizumab therapy was continued after stereotactic radiosurgery; however, his condition deteriorated, and he transitioned into hospice care, where he died of disease 9 months following initial diagnosis.

DISCUSSION

MCC-UP occurring in the immunosuppressed state is a rare presentation of MCC.

At our institution, we have encountered only 2 cases of 700 MCC patients in the period of 2006-2020. So far, 6 cases have been reported (Table II).[7-9] One case series reports that up to 4% of MCC-UP can present with immunosuppression; however, this data may be an overestimate due to publication and/or sampling biases.[3,5] For comparison, the incidence of melanoma of unknown primary tumor occurring in immunosuppressed patients has been reported at 2%.[10]

MCC-UP in the setting of immunosuppression has some similarities to MCC-UP. MCC-UP is more common in men and Caucasian patients.[5] Of reported cases of MCC-UP in the setting of immunosuppression for which sex was reported, 6/7 (86%) were men. In most of the cases, data on race were not reported. Previous reports of MCC-UP suggest that a majority (78%) of patients present with nodal disease only (stage IIIA), most commonly inguinal.[3] For MCC-UP in the setting of immunosuppression, 4/7 (57%) cases presented with nodal disease only (Table II).

MCC-UP in the setting of immunosuppression appears to have a distinct clinical course compared with MCC-UP, including younger age of presentation and worse prognosis. Among reported cases for which age at diagnosis was reported, the average age of diagnosis was 48.9 years, and 5/7 cases (71%) were diagnosed prior to 50 years of age, with death from disease or persistent disease noted in 5/7 cases (71%) with follow-up data. This is in contrast to an improved MCC-specific survival for MCC-UP versus MCC-KP patients ($P < .001$) and no significant difference in age at diagnosis between these patient groups, with 90% of cases diagnosed after the age of 50 years.[1,5]

The distinct natural history for MCC-UP in the setting of immunosuppression may be due to the presence of immunosuppression, which has been shown to be associated with earlier disease onset and worse clinical outcomes.[1] Poor prognosis may also be associated with negative MCPyV status or low-to-absent CD8+ tumor-infiltrating lymphocytes, both of which were noted in our two cases.[11] It should be noted that a majority of MCC patients exhibit low-to-absent intratumoral infiltration by CD8+ lymphocytes; however, those with high levels appear to experience superior disease-specific survival.[11] Notably, only 1 other published case of MCC-UP in the setting of immunosuppression has

Table II. Reported cases of Merkel cell carcinoma (MCC) with unknown primary tumor (MCC-UP) in the setting of immunosuppression

Reference (year)	Age, sex, race	Site(s) of metastasis	Condition	Immunosuppression (duration)	MCV status (+/-)	Treatment	Clinical status, duration (months)
Samarendra et al (2000)[14]	40, M, Caucasian	Inguinal LN*	HIV	CD4 = 160/mm^3 VL = 11,000 copies/mL (3 years‡)	NA	Excision	ANED, 42
Kaisar et al (2007)[7]	67, F, NA	Axillary LN*, liver*, bone marrow†	Renal transplant	Sirolimus, cyclosporine, prednisolone (6 years)	NA	Palliative care	DOD, NA
Ottaviani et al (2010)[8]	41, M, NA	Parotid LN*, liver†	HIV	CD4 = 708/mm^3 VL = NA (20 years‡)	NA	Partial parotidectomy, adj-RT, adj-CTX	DOD, 14
Brugnaro et al (2011)[9]	66, M, NA	Inguinal LN*	HIV	CD4 = 479/mm^3 VL = 0-40 copies/mL (24 years‡)	NA	Excision, adj-RT, adj-CTX, sal-CTX	ANED, 24
Tarantola et al (2013)[3]	NA, NA, NA	NA	Solid organ transplant NOS	NA	NA	NA	NA
Li et al (2018)[12]	33, M, Hispanic	Axillary LN*, pancreas*	HIV	NA	+	CTX, ITX, pal-RT	AWD, NA
Present case	47, M, Caucasian	Neck LN*	Lung transplant	Azathioprine, cyclosporine, prednisone (3 years)	−	Left side of the head/neck: ND + adj-RT; partial parotidectomy +NE; rev-ND; re-RT Left axilla: ALND + adj-RT; Right side of the head/neck: parotidectomy, ND, ALND	AWD, 33
Present case	48, M, Caucasian	Inguinal LN*, liver*	Renal transplant	Azathioprine, cyclosporine, prednisone (29 years)	−	CTX, ITX, SRS	DOD, 9

adj-RT, Adjuvant radiation therapy; *ALND*, axillary lymph node dissection; *ANED*, alive with no evidence of disease; *AWD*, alive with disease; *CTX*, chemotherapy; *DOD*, died of disease; *F*, female; *ITX*, immunotherapy; *LN*, = lymph node; *M*, male; *NA*, not available/not reported; *ND*, neck dissection; *NE*, neck exploration; *NOS*, not otherwise specified; *pal-RT*, palliative radiation therapy; *rev-ND*, revision neck dissection; *re-RT*, re-irradiation; *sal-CTX*, salvage chemotherapy; *SRS*, stereotactic radiosurgery; *VL*, viral load (HIV).

*Metastasis present on initial presentation.

†Metastasis following disease progression.

‡Duration of active HIV infection.

included testing for MCPyV, and the test was positive.[12] Previously, MCC-UP has been shown to have a significantly lower association with MCPyV compared to MCC-KP; however, conflicting reports exist.[5,9]

To our knowledge, this is the first report to demonstrate the lack of tumor-infiltrating lymphocytes and provide genomic analysis of MCC-UP in immunosuppression. Mutation analysis available for one viral negative tumor confirmed the presence of *RB1* and *NOTCH1* mutations previously described in virus-negative MCC.[1] However, unlike the majority of MCPyV-negative MCC, this tumor lacked mutation in *TP53*, raising the question whether MCC-UP in the setting of immunosuppression harbors the full complement of genomic changes reported in other MCC tumors. In this case, copy gain of *MDM4* might represent an alternative mechanism for inactivation of *TP53*, as previously described in MCC.[13] The limited coverage of our gene panel did not allow formal evaluation for the UV mutation signature.

The paradoxical combination of immunosuppression and MCC-UP has led some to argue for the possible existence of a noncutaneous primary lesion, such as MCC arising *de novo* within a lymph node.[13] Despite the unknown cellular origins of MCC itself, this possibility remains unlikely given the high incidence of UV-related DNA damage and MCPyV positivity found in MCC-UP, both supporting a cutaneous origin.[5] Similarly, a prior case has reported MCPyV positivity in MCC-UP in an immunosuppressed patient.[12]

Another theory reconciling the coexistence of MCC-UP and immunosuppression relates to differences in the nature of immunosuppression. Reports on immunosuppression in the setting of MCC suggest that solid organ transplantation (SOT) is among the most common immunosuppression subtypes, whereas HIV is amongst the least common.[15] In our review of MCC-UP in the setting of immunosuppression, four cases (50%) involved SOT, and the remaining 4 (50%) involved HIV. Since both SOT and HIV primarily cause a weakened cell-mediated immune response, it is possible that intact humoral immunity provides an immune response capable of regressing the primary lesion.

In summary, MCC-UP in the setting of immunosuppression is a rare presentation of MCC, the existence of which dermatologists should be aware. Cases can be either MCPyV-positive or -negative and may exhibit low-to-absent CD8+ tumor-infiltrating lymphocytes, consistent with a background of immunosuppression. Patients with MCC-UP in the setting of immunosuppression are younger at disease onset and have a worse prognosis compared with those presenting with MCC-UP. Further understanding of this clinical entity yields insight into disease mechanisms.

Conflicts of interest

None disclosed.

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