CASE REPORT

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

Jason M. Rizzo, MD, PhD,a Paul W. Harms, MD, PhD,a,b,c Kelly L. Harms, MD, PhD,a,b Andrew Plaska, MD,a Chad Brenner, PhD,b,d,e and Alison B. Durham, MD,a,b
Ann Arbor, Michigan

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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.

From the Department of Dermatology,a Rogel Comprehensive Cancer Center,a Department of Pathology,b Program in Cellular and Molecular Biology, and Department of Otolaryngology - Head and Neck Surgery, University of Michigan Medical School, Ann Arbor.

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Correspondence to: Alison B. Durham, MD, University of Michigan - Michigan Medicine, Department of Dermatology, 1910 Taubman Center, 1500 E, Medical Center Drive, Ann Arbor, MI 48109-5314. E-mail: ambates@med.umich.edu.

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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 I).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.5 For comparison, the incidence of melanoma of unknown primary tumor occurring in immunosuppressed patients has been reported at 2%.10

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 | AJCCy 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. yAmerican Joint Committee on Cancer (AJCC) TNM Staging Classification for Merkel Cell Carcinoma (8th ed., 2017).
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) | 40, M, Caucasian | Inguinal LN* | HIV | CD4 = 160/mm³  
VL = 11,000 copies/mL  
(3 years³) | NA | Excision | ANED, 42 |
| Kaisar et al (2007) | 67, F, NA | Axillary LN*, liver*, bone marrow¹ | Renal transplant | Sirolimus, cyclosporine, prednisolone (6 years) | NA | Palliative care | DOD, NA |
| Ottaviani et al (2010) | 41, M, NA | Parotid LN*, liver* | HIV | CD4 = 708/mm³  
VL = NA (20 years¹) | NA | Partial parotidectomy, adj-RT, adj-CTX | DOD, 14 |
| Brugnaro et al (2011) | 66, M, NA | Inguinal LN* | HIV | CD4 = 479/mm³  
VL = 0-40 copies/mL  
(24 years¹) | NA | Excision, adj-RT, adj-CTX, sal-CTX | ANED, 24 |
| Tarantola et al (2013) | NA, NA, NA | NA | Solid organ transplant NOS | NA | NA | NA | NA |
| Li et al (2018) | 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; parotidectomy + NE; rev-ND; re-RT | 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).

¹Metastasis present on initial presentation.
²Metastasis following disease progression.
³Duration 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.\(^{14}\) 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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