Immune checkpoint inhibitor therapy in HIV-associated Merkel cell carcinoma: A case series of 3 patients

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INTRODUCTION

Merkel cell carcinoma (MCC) is an aggressive skin cancer, which is about twice as likely to metastasize as compared with melanoma.1 There are 2 distinct biological pathways for developing MCC: Merkel cell polyomavirus (MCPyV)-induced and ultraviolet light-induced.2 In individuals immunosuppressed by HIV infection, the risk of developing MCC is 13-fold higher than for the general population.1 Historically, outcomes have been dismal, with a 2-year disease-specific survival rate of 0% in 1 published case series.3

Recently, anti-programmed cell death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1) agents in immunocompetent patients with advanced MCC (aMCC) demonstrated a ~60% response rate and a durable benefit in the majority of responding patients.4 Based on these data, these agents have emerged as the treatment of choice for aMCC. However, immunosuppressed individuals, including those who are HIV-positive, have been excluded from clinical trials with anti-PD-(L)1 agents due to concerns about efficacy and potential for inadvertent augmentation of infectious and/or inflammatory activity.5 It is, therefore, unknown whether immune checkpoint inhibitors (ICI), including anti-PD-(L)1 treatment, are effective for HIV-positive patients with aMCC.

CASE REPORT

Among the ~1500 MCC patients diagnosed between 1980 and 2020, we identified 10 patients with a history of HIV at the time of their MCC diagnosis. Distant metastatic disease eventually developed in all the 10 patients. Among these patients, 3 were treated with ICI therapy.

To better understand the clinical and biological features of HIV-positive aMCC patients treated with ICI, we performed a comprehensive review of our Seattle-based IRB-approved repository of MCC patient data and specimens. We have also described biomarker analyses, including immune cell infiltration, tumor MCPyV status, and intratumoral expression of PD-1 and PD-L1.

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IRB approval status: All studies were performed in accordance with the Helsinki principles and were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center (IRB #6585). All patients included in this study provided informed consent for their clinical data to be analyzed for research purposes.

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Patient 1

Patient 1 was a 55-year-old man who was initially diagnosed with MCC involving the right neck and parotid gland. The patient underwent a parotidectomy and neck dissection, followed by adjuvant radiation treatment (RT) of both the right parotid and right side of the neck. Ten months after diagnosis, metastatic disease developed in the patient’s abdomen and peritoneum.

The patient was diagnosed with HIV 30 years earlier. Over this period, he had been treated with an antiretroviral regimen consisting of ritonavir, darunavir, raltegravir, emtricitabine, tenofovir, and alafenamide. His HIV viral load was consistently undetectable; however, his CD4 count persistently remained in the AIDS-defining range of 150-200 cells/mm³. He had a history of oral candidiasis but no other recent AIDS-defining illnesses.

The patient was offered pembrolizumab every 3 weeks. A positron emission tomography/computed tomography (PET/CT) scan following 4 cycles showed a complete response (CR) with resolution of PET-avid disease (Fig 1, A, B). Besides grade 1 fatigue, the patient tolerated immunotherapy well without any major side effects. After 26 months of treatment and maintaining a CR, the patient decided to stop infusions. Three months later, the patient restarted pembrolizumab, when he developed a minimally fluorodeoxyglucose-PET-avid lesion in the right aspect of the neck. The patient’s previous MCC was highly fluorodeoxyglucose-avid at diagnosis (typical for MCC in general), but pembrolizumab was restarted for possible disease recurrence. Biopsy was not performed as per the patient’s wish. In the PET/CT 4 months later, the right neck lesion remained stable, but it resolved 1 year later. Since resuming pembrolizumab, he has remained without clinically detectable disease at 45 months from the initial diagnosis of metastasis. His HIV status and CD4 levels are stable, and his viral load remained undetectable throughout his treatment course.

Biomarker and immunohistochemistry (IHC) analysis of the pretreatment tumor biopsy samples of his aMCC were performed in the same manner as for patient 1. Intratumoral CD8⁺ (infiltration score of 2; 180-433 cells/mm³) and CD4⁺ T cells were observed (7 cells/mm² intratumorally) (Fig 1, G, H). Tumor biopsy sections were positive for expression of PD-1 and PD-L1 (Fig 2, H, I). IHC expression of MCPyV large T antigen was positive (Fig 2, G).

Patient 2

Patient 2 was a 64-year-old man who was initially diagnosed with MCC involving a 6-cm tumor of the left buttock, which spread to the ipsilateral inguinal lymph nodes. The patient underwent removal of the involved lymph nodes, followed by RT. Nine months after the initial diagnosis, metastatic disease developed in the left leg muscles and adenopathy along the left iliac chain and retroperitoneum.

The patient’s HIV infection had been diagnosed >30 years earlier. Antiretroviral therapy included darunavir, dolutegravir, and raltegravir. The HIV viral load was consistently undetectable, with a stable CD4 count between 1500 and 1600 cells/mm³. The patient experienced a decrease in the CD4 count to 500 cells/mm³ after RT, which gradually recovered to about 700 cells/mm³.

The patient received pembrolizumab every 3 weeks. A CT scan following 5 cycles of immunotherapy showed CR (Fig 1, E, F). The patient tolerated the treatment well without any major side effects. He continues to have no detectable disease after 22 months of pembrolizumab treatment. His HIV status and CD4 levels are stable, and his viral load remained undetectable throughout the treatment course.

Biomarker and IHC analyses of the pretreatment tumor biopsy samples of his aMCC were performed in the same manner as for patient 1. Intratumoral CD8⁺ (infiltration score of 3; 434-582 cells/mm³) and CD4⁺ T cells were observed (12 cells/mm² intratumorally) (Fig 1, C, D). Furthermore, tumor biopsy sections were positive for PD-1 and PD-L1 expression (Fig 2, D, E). IHC expression of MCPyV large T antigen (Santa Cruz Biotechnology clone CM2B4) was negative, which suggests that the patient’s MCC tumor was virus-negative MCC (Fig 2, C).

Patient 3

Patient 3 was a 64-year-old man who was initially diagnosed with MCC of the posterior scalp with microscopic involvement of the ipsilateral neck lymph nodes. The patient underwent wide local excision of the primary lesion, sentinel lymph node biopsy, and RT of the scalp and neck. However, his disease continued, and multiple lesions developed on his scalp, liver, and bone lesions. He received an 8-Grey single-fraction RT to the skin lesions, followed by 2 cycles of chemotherapy with carboplatin and etoposide with short-term benefit.

The patient’s HIV infection had been diagnosed 9 years before and was treated with
efavirenz-emtricitabine-tenofovir. His HIV viral load remained consistently undetectable, with a stable CD4 count between 500 and 700 cells/mm³.

Within 2 months of completion of chemotherapy, the patient's disease progressed, and he started pembrolizumab. The patient's MCC continued progressing, despite the addition 1 dose of ipilimumab. Radioactive sphere embolization of the liver was added one month later, with continued infusion of pembrolizumab every 3 weeks. Despite multiple lines of immunotherapy, the patient’s MCC progressed. Unfortunately, his disease did not

![Fig 1. Changes in patient 1 MCC tumor size in the right aspect of the mid-abdomen (2.6 × 1.7 cm), which resolved after 4 doses of pembrolizumab treatment (A, B), and IHC of pretreatment tissue demonstrating moderate intratumoral CD4+ and CD8+ immune infiltrate (C, D). Changes in patient 2 MCC tumors near the aortoiliac bifurcation (L, 2.9 × 1.5 cm; R, 2.5 × 2.2 cm), which resolved after 10 months of pembrolizumab treatment (E, F), and IHC stains demonstrating intratumoral CD4+ and CD8+ immune infiltrate (G, H). IHC, Immunohistochemistry; MCC, Merkel cell carcinoma.](image-url)
respond to subsequent therapies, and the patient succumbed to disease 4 months after initiating pembrolizumab. His MCC was MCPyV-positive, which was confirmed by an MCPyV-specific oncoprotein antibody test. Tumor tissue was not available for analysis.
<table>
<thead>
<tr>
<th>References</th>
<th>Age (y)</th>
<th>Sex</th>
<th>ECOG</th>
<th>Treatment</th>
<th>Prior systemic therapy</th>
<th>CD4 counts at start of treatment (copies/ml)</th>
<th>First diagnosis of HIV</th>
<th>Antiretroviral therapy</th>
<th>Viral load during ICI (copies/mL)</th>
<th>IRAEs</th>
<th>Best response</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>55</td>
<td>M</td>
<td>0</td>
<td>Pembrolizumab 2 mg/kg q3w</td>
<td>None</td>
<td>Undetectable</td>
<td>150-200 (remained stable during ICI)</td>
<td>30 years before ICI</td>
<td>Ritonavir, darunavir, efavirenz, tenofovir, alafenamide</td>
<td>Undetectable</td>
<td>Grade 1 fatigue</td>
<td>CR</td>
<td>26*</td>
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<tr>
<td>Patient 2</td>
<td>64</td>
<td>M</td>
<td>0</td>
<td>Pembrolizumab 2 mg/kg q3w</td>
<td>None</td>
<td>Undetectable</td>
<td>500-700 (remained stable during ICI)</td>
<td>30 years before ICI</td>
<td>Darunavir, dolutegravir, efavirenz, emtricitabine-tenofovir</td>
<td>Undetectable</td>
<td>None</td>
<td>CR</td>
<td>22</td>
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<tr>
<td>Patient 3</td>
<td>64</td>
<td>M</td>
<td>0</td>
<td>Pembrolizumab 2 mg/kg q3w, ipilimumab 50 mg, 1 dose cisplatin and etoposide</td>
<td>Undetectable</td>
<td>500-700 (remained stable during ICI)</td>
<td>9 years before ICI</td>
<td>Darunavir, dolutegravir, efavirenz, emtricitabine-tenofovir</td>
<td>Undetectable</td>
<td>None</td>
<td>PD</td>
<td>0</td>
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<td>Heppt et al, 2017</td>
<td>58</td>
<td>M</td>
<td>0</td>
<td>Pembrolizumab 2 mg/kg q3w</td>
<td>liposomal doxorubicin</td>
<td>20</td>
<td>(increased to 223 during ICI)</td>
<td>6 months before ICI</td>
<td>Emtricitabine, tenofovir, dolutegravir</td>
<td>54 at 3 mo, 102 at 6 months, and &lt;20 at 12 mo from ICI unknown</td>
<td>Grade 1 pneumonitis</td>
<td>CR</td>
<td>8</td>
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<td>Homsi et al, 2018</td>
<td>39</td>
<td>M</td>
<td>0</td>
<td>Avelumab 10 mg/kg q 2w</td>
<td>cisplatin and etoposide</td>
<td>&gt;110,000, decreased to 200 after antiretroviral therapy</td>
<td>Unknown</td>
<td>Details unknown (during work-up for MCC diagnosis)</td>
<td>Unknown</td>
<td>Grade 2 thyroiditis and hypothyroidism</td>
<td>CR</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Linge et al, 2018</td>
<td>60</td>
<td>M</td>
<td>0-1</td>
<td>Pembrolizumab 2 mg/kg q3w, followed by avelumab 10 mg/kg q2w</td>
<td>adjuvant doxorubicin</td>
<td>127,000</td>
<td>(increased to 238 during ICI)</td>
<td>6 months before initial ICI (during screening for a trial)</td>
<td>Emtricitabine, tenofovir, dolutegravir</td>
<td>42 at 18 mo from ICI</td>
<td>Unknown</td>
<td>PD on pembrolizumab, avelumab was in adjuvant</td>
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</table>

CR, Complete response; ECOG, Eastern Cooperative Oncology Group; F, female; ICI, immune checkpoint inhibitor; IRAEs, immune-related adverse events; M, male; MCC, Merkel cell carcinoma; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

*After 26 months of pembrolizumab treatment and maintaining a CR, the patient stopped infusions. An fluorodeoxyglucose-PET-avid lesion developed in the right side of his neck 3 months later. The lesion was not biopsied, and patient resumed pembrolizumab. The neck lesion in the right side remained stable in the subsequent PET/CT scans and had resolved 1 year later. The patient remains with no clinically detectable disease at 45 months from the initial diagnosis of metastatic disease.
DISCUSSION

While anti-PD-(L)1 agents have become a standard treatment for aMCC, HIV-positive patients have been excluded from most previous trials. Therefore, limited data exist in terms of ICI use for HIV-positive patients with aMCC.

In our cohort of ~1500 MCC patients, we identified 3 individuals with chronic HIV infection treated with ICIs for aMCC. Despite a chronic AIDS-defining low CD4+ count, patient 1 experienced a durable CR without any HIV or immune-related complications. Interestingly, despite the HIV status, the patients whose MCC disease responded to ICIs both had an immune-favorable MCC tumor microenvironment, including a CD8+ infiltrated pattern of T cells and PD-L1 expression of greater than 1%.

Unfortunately, one individual’s disease (patient 3) progressed on multiple lines of ICI. It is possible that bone marrow suppression, caused by 2 initial cycles of chemotherapy, may have affected his response to ICI. Multiple studies have shown that the response rate to anti-PD-(L)1 agents after chemotherapy is lower than for first-line systemic treatment in immunocompetent patients.4 It is therefore plausible that HIV-positive patients have a more beneficial response to anti-PD-(L)1 for their aMCC, if it is used as a first-line treatment.

Three other case reports in the literature describe anti-PD-(L)1 responses for aMCC in patients with HIV (Table I).10-12 To the best of our knowledge, the cases reported here represent the longest follow-up to date.

While we cannot estimate the overall response rate based on our small number of cases, our data do support that HIV-positive MCC patients can experience favorable responses to anti-PD-(L)1 agents. This is further supported by a recent systematic review of case reports of ICI use across different malignancies, which found that ICIs had similar objective responses in HIV-positive patients when compared with HIV-negative patients.13

Pembrolizumab has been used for the treatment of other cancers in individuals with HIV, and early reports from the CITN-12 trial suggest that toxicity is tolerable in those with HIV.14 Given the rarity of both HIV and MCC, very few cases are observed in the US, and a large prospective trial is not feasible. However, given the demonstrated 0% MCC-specific 2-year survival among 7 patients with HIV treated with prior approaches,3 we believe that these findings provide support for the use of PD-(L)1 inhibitors in the first-line in patients with HIV and aMCC.

Conflicts of interest

Dr Nghiem has received consulting fees from EMD Serono, Pfizer, Sanofi/Regeneron, and 4SC and research grant support from Bristol-Meyers Squibb. Dr Paulson has received research grant support from EMD Serono, Bluebird Biosciences, and Merck. Dr Lewis has received consulting fees from Merck and Regeneron and research grant support from Bristol-Meyers Squibb, Merck, Regeneron, and EMD Serono. Author Alexander and Drs Park, Church, Shinohara, Lewis, and Lee have no conflicts of interest to declare.

REFERENCES