CASE REPORT

A Case Report of Leptomeningeal Carcinomatosis Secondary to Recurrent Merkel Cell Carcinoma after Avelumab

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ABSTRACT
Introduction: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine cancer with a high mortality rate of 33% to 46%. Merkel cell is a type of epidermis cell receptor responsible for contact sensitivity and is known to have neuroendocrine properties. Treatment of Merkel cell carcinoma with avelumab has been promising, but its rarity and poor prognosis necessitates close follow up.

Case Presentation: A 71-year-old woman presented with a left forearm mass that was initially suspected to be a sebaceous cyst. After surgical excision and biopsy, she was diagnosed with Merkel cell carcinoma. The patient underwent avelumab treatment for 2 years, with remission of cancer for 24 months. A positron emission tomographic scan at 24 months of treatment noted uptake in the left axilla and portocaval regions. Despite receiving different combinations of immunotherapy, chemotherapy, and radiation, the patient's cancer metastasized to the leptomeninges. She was transitioned to hospice and passed away 3 months after diagnosis of leptomeningeal carcinoma.

Conclusion: This case highlights the efficacy of avelumab in keeping patients in remission, which can offer increased quality of life. However, it also highlights the aggressive nature of Merkel cell carcinoma and the importance of surveillance for early detection of recurrence.

INTRODUCTION

Merkel cell is a type of epidermis cell receptor responsible for contact sensitivity and is known to have neuroendocrine properties. MCC is a rare and aggressive neuroendocrine cancer that, if untreated, can be fatal.2 Although extremely rare, it can metastasize to the leptomeninges. This metastasis occurs by seeding of tumor cells into the cerebrospinal fluid (CSF) and the leptomeninges as a terminal, late-stage complication of various solid tumors.3 MCC usually presents as a painless lump, which can delay early detection and treatment. Risk factors for MCC include the following: age (> 50 years old), excessive ultraviolet light exposure, smoking, immunocompromised status, and history of infection with Merkel cell polyomavirus.4-7 MCC has been increasing in occurrence, has a high mortality rate, and lacks a response to traditional chemotherapy.8,9 Fortunately, avelumab—a programmed cell death protein 1/programmed cell death–ligand 1 blocking antibody—obtained accelerated approval by the US Food and Drug Administration in 2017 for treatment of MCC as a result of its success in study trials. Unlike traditional chemotherapy, however, there are currently no known studies on avelumab and the prevention or treatment of metastatic MCC to the leptomeninges.9 As a novel monotherapy treatment agent for MCC, currently the standard of care, there is limited knowledge of this medication. Thus, additional studies are needed, especially in evaluating the rare occurrence of metastatic leptomeningeal carcinomatosis secondary to MCC after avelumab treatment. For Case Presentation outline, please refer to Table 1.

CASE PRESENTATION

A 71-year-old Hispanic woman with a history of diabetes and high blood pressure presented to her primary physician with a painless left proximal forearm nodule that had increased slowly in size for the past 6 months. It was diagnosed initially as a sebaceous cyst. The patient opted for localized excision of the presumed sebaceous cyst. Afterward, the patient completed localized radiation in the left proximal forearm as recommended. Six months after localized radiation, the patient noted a left distal humerus mass (Figure 1). A computed tomographic scan of left distal humerus without contrast showed a 2.6 × 2.5 × 1.9-cm subcutaneous soft tissue mass compatible with metastatic disease. A positron emission tomographic (PET) scan showed left distal humerus lymph node uptake, and left axillary and left subpectoral lymph node uptake. The patient underwent left distal humerus mass excision and left axillary lymph node dissection. Pathology confirmed 7 of the 14 left axillary lymph nodes were consistent with metastatic MCC. A follow-up computed tomographic scan was taken of the chest after the surgical resection of the left subpectoral and left axillary lymph nodes, and it showed a retained 1.2 × 1-cm left subpectoral cancerous lymph node.

The patient then completed avelumab treatment biweekly for 24 months (with diphenhydramine and acetaminophen prior to each treatment) for T4N1M1 disease.

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<table>
<thead>
<tr>
<th>Date</th>
<th>Summaries from initial and follow-up visits (patient's primary concerns as well as clinical-initiated diagnostic assessments and diagnoses)</th>
<th>Diagnostic testing, including dates of relevant testing, such as laboratory, imaging, or surveys</th>
<th>Interventions (pharmaceuticals and dietary supplements, dietary and lifestyle recommendations, procedures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/27/2016</td>
<td>Patient had left forearm nodule discomfort and was referred to general surgery by the primary doctor for excision.</td>
<td>Pathology showed neuroendocrine tumor consistent with Merkel cell cancer.</td>
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<tr>
<td>11/10/2016</td>
<td>Patient was referred to imaging for cancer evaluation.</td>
<td>CT scan of abdomen and pelvis showed no masses.</td>
<td>General surgery completed a wide-excision biopsy of the left forearm with antecubital lymph node biopsy.</td>
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<tr>
<td>11/14/2016</td>
<td>Patient was referred to imaging for cancer evaluation.</td>
<td>CT scan of the chest showed no masses.</td>
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<td>12/1/2016</td>
<td></td>
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<tr>
<td>12/2016–01/2017</td>
<td>Received localized radiation to the left forearm, weekly, for 10 wk.</td>
<td>Physical exam was conducted and was within normal limits during treatment.</td>
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<td>9/1/2017</td>
<td>At radiation follow-up visit, the patient presented with 6 wk of a left nontender elbow mass that was increasing in size.</td>
<td>Imaging was ordered for left elbow mass and metastatic cancer evaluation.</td>
<td>A follow-up PET scan was ordered for metastatic cancer evaluation.</td>
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<tr>
<td>9/8/2017</td>
<td>CT scan of left elbow mass identified on 9/1/2017 radiation follow-up visit showed mass and enlarged axillary lymph node.</td>
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<td>9/19/2017</td>
<td>PET scan showed a positive uptake at the medial left elbow, left axilla, and left subpectoral lymph nodes.</td>
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<tr>
<td>9/27/2017</td>
<td>Patient underwent general surgery for biopsies of recurrent mass.</td>
<td>Biopsies were performed on the left elbow and axillary. Pathology confirmed the presence of Merkel cell carcinoma.</td>
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<tr>
<td>10/2017</td>
<td>Patient began radiation to the left elbow area concurrently with avelumab.</td>
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<td>Avelumab was administered for 24 mo without any side effects and with negative PET scans.</td>
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<td>10/2019</td>
<td>The PET scan obtained at the 24-mo avelumab treatment was positive for left subclavian and porta hepatitis adenopathy.</td>
<td>Patient was placed on ipilimumab and nivolumab, and began localized radiotherapy to the left upper chest and abdomen area.</td>
<td>Patient was started on proton pump inhibitors, liquid antacids, and antiemetics as needed as a result of gastitis, which was most likely induced by the radiation.</td>
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<tr>
<td>12/28/2020–2/3/2020</td>
<td>Patient was admitted for bilateral leg and hand weakness.</td>
<td>Patient was diagnosed with GBS and was treated with intravenous immunoglobulin. The lumbar puncture for GBS syndrome incidentally was positive for Merkel cells. MRI of lumbar spine showed subtle enhancement of anterior thoracolumbar spinal cord T12-L1. Results were unable to confirm GBS or leptomeningeal disease.</td>
<td>Patient's strength recovered. Ipilimumab and nivolumab were discontinued at this point because of a concern of spread of cancer into meninges. At this point, the patient was pending a new treatment plan.</td>
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<td>2/17/2020–2/27/2020</td>
<td>Patient was admitted for headache, nausea, vomiting, and back pain.</td>
<td>While the patient was being evaluated for a headache, it was noted the patient was hypertensive and had a cranial nerve 12 palsy. These findings were concerning for leptomeningeal disease. While the patient was being evaluated for nausea and vomiting, an endoscopy/sigmoidoscopy was performed and showed gastric ulcers and immune-mediated colitis While the patient was being evaluated for back pain, MRI of the lumbar spine showed leptomeningeal involvement. Incidentally, during hospitalization, the patient was found to have urinary retention that was attributed to leptomeningeal involvement.</td>
<td>Hypertension was treated with losartan, amlodipine, and lisinopril during hospitalization, and the patient was later discharged with these medications. Leptomeningeal involvement was treated with brain radiation, carboplatin, and 1 dose of etoposide, followed by cisplatin after discharge. During hospitalization, the patient was started on omeprazole and sucralfate (as needed) for gastitis, Senokot and Miralax (as needed) for constipation, and a bland diet. The patient was discharged with these recommendations. Patient received hydrocodone/acetaminophen (as needed during hospitalization)</td>
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Follow-up PET scans during avelumab treatment were negative for uptake, including at the retained lymph node. A PET scan at 24 months of treatment with avelumab showed a recurrence of MCC to a left subpectoral lymph node (Figure 2) and the left portacaval region (Figure 3).

The patient completed localized radiation to the left subpectoral and portocaval regions, and was started on nivolumab and ipilimumab. A follow-up PET scan after completion of radiation and while taking nivolumab and ipilimumab showed a positive treatment response resulting from decreased size and intensity of fluorodeoxyglucose uptake in both locations.

The patient was hospitalized for ascending bilateral leg and arm weakness, and diagnosed with Guillain Barré syndrome 27 months after diagnosis of MCC. This was most likely secondary to nivolumab and ipilimumab, and the patient's symptoms improved with intravenous immunoglobulin, hydrocortisone treatment, and discontinuation of nivolumab and ipilimumab. CSF cytology was positive for MCC, and magnetic resonance imaging (MRI) of the lumbar spine revealed leptomeningeal carcinomatosis.

The patient then developed hypertension, headache, cranial nerve 12 palsy, and low-back and right-leg pain 14 days after Guillain Barré syndrome hospitalization. The patient's hypertension, headache, cranial nerve 12 palsy, and back and leg pain were attributed to her leptomeningeal disease. The patient's nausea, vomiting, and abdominal pain were secondary to gastric ulcer seen via endoscopy (most likely radiation induced), immune checkpoint inhibitor-related colitis (based on sigmoidoscopy biopsy), and urinary retention secondary to neurogenic bladder. The patient received only 1 treatment of carboplatin and etoposide during hospitalization, and completed whole-brain and lower thoracic–lumbar radiation for leptomeningeal disease.

The patient then improved and was discharged with a medication regimen for blood pressure control and symptomatic management.

Shortly after hospital discharge, the patient developed severe right-arm incoordination secondary to leptomeningeal disease and underwent radiation to the cervical spine, after which symptoms improved. The patient then began weekly cisplatin chemotherapy, but she continued to decline neurologically. The patient again developed bilateral lower leg weakness with inability to bear weight, became bed bound, had transient episodes of diplopia, developed left cranial nerve 6 palsy, and had 1 episode of seizure-like activity, and eventually transitioned to hospice.

**DISCUSSION**

This appears to be the first published case of leptomeningeal carcinomatosis secondary to recurrent MCC treated with avelumab. Extensive PubMed research did not yield any additional case reports of a similar occurrence. This patient's
risk factors for MCC include age and ultraviolet exposure. Initial surgery and radiation for stage 1 MCC include wide excision surgery and/or localized radiation. However, 8 months later, despite surgery and radiation, the patient had recurrence of MCC on left elbow, with distal lymph node involvement. Treatment for recurrence of MCC includes immunotherapy. The patient completed biweekly avelumab treatments for 24 months with no adverse events; however, a follow-up PET scan at 24 months showed metastatic MCC to the left chest and portocaval regions. The patient completed radiation to the chest and portocaval regions, and started nivolumab and ipilimumab treatment, with a positive response seen on follow-up imaging. The patient subsequently developed GBS, leading to an incidental finding of malignant cells in the CSF, with MRI confirmation of leptomeningeal carcinomatosis. Ipilimumab and nivolumab were discontinued, and the patient was then switched to cisplatin. Despite eventually completing whole-brain, cervical, thoracic, and lumbar spine radiation for her leptomeningeal disease symptoms, the patient continued to decline neurologically.

The last known reported case of leptomeningeal MCC was documented in 2011. It is a rare and aggressive form of cancer, with an estimated incidence of about 800 cases per year in the US, and 2- and 5-year overall survival rates of 53.9% and 32.8%, respectively. The incidence of leptomeningeal carcinomatosis secondary to MCC is extremely rare, with a short life expectancy of weeks to months. Leptomeningeal disease can present as cranial nerve deficits, radicular pain, headache, back pain, visual disturbance, diplopia, hearing loss, psychiatric disorders, seizures, or cauda equina syndrome. The diagnosis of leptomeningeal carcinomatosis is made by CSF analysis and MRI. Malignant cells, pleocytosis, high protein levels, or low glucose are often seen in the CSF. MRI with gadolinium should include the brain and spine because the disease can affect the entire neuraxis, versus computed tomography, which is less sensitive in detecting leptomeningeal cancer. The introduction of avelumab was seen as a promising agent to fight MCC (local or distant) and has increased the survival rate as well as the quality of life when compared to chemotherapy. Our patient achieved both quality and quantity of life with avelumab. However, despite taking avelumab, she developed metastatic leptomeningeal cancer. Treatment for
leptomeningeal cancer may include radiation, intrathecal chemotherapy, systemic chemotherapy, or surgery. The patient received whole-brain radiotherapy, focal radiotherapy in different areas of the spine for palliative relief, and systemic chemotherapy because she experienced various symptoms associated with leptomeningeal cancer. She survived her leptomeningeal disease for 3 months despite these treatment efforts. This case highlights the importance of surveillance while taking avelumab and its limitations with regard to blood–brain barrier permeability because, although rare, MCC can disseminate into the leptomeninges.

This case also highlights the efficacy of avelumab in keeping patients in remission, which can offer increased quality of life. The case also underscores the importance of surveillance for relapse and early detection of recurrent MCC. With the constant advancement of research, this case may highlight ways that avelumab can be used and patients can be monitored to maintain remission status and increase life expectancy.

CONCLUSION

This case highlights 3 key points: 1) the importance of close follow-up visits, especially with localized cancer, for the prevention and early detection of metastatic disease; 2) a rare side effect of immune checkpoint inhibitor causing GBS; and 3) despite the use of avelumab (recently approved by US Food and Drug Administration) for MCC, leptomeningeal involvement, although rare, can occur and should be considered in those patients who present with symptoms of meningeal involvement such as headache, back pain, or neurologic symptoms.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Authors’ Contributions

Pedro Mendoza collected the information and wrote the manuscript with the assistance of Kathy Chuang, MD. Both researched, analyzed, and interpreted the information for publication.

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References