Medical Case Report

Concurrent Merkel Cell Carcinoma and Melanoma in Individual Patients Presents a Treatment Challenge: A Case Series

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Clinical Practice Points

- Melanoma and Merkel cell carcinoma (MCC) are rare, but aggressive, skin cancers that, in part, share etiologies.
- Locoregional melanoma and MCC are managed with surgery, with or without postoperative radiotherapy; however, patients with advanced melanoma and MCC require targeted therapy and/or immunotherapy for melanoma and chemotherapy with or without immunotherapy for MCC.
- We present patients with both malignancies, discuss the treatment challenges, and highlight the role of programmed cell death 1 (PD-1) inhibition in disease management.
- We describe 8 patients (6 men) with a median age at diagnosis of 65 years for melanoma and 76 years for MCC.
- Melanoma and MCC were diagnosed simultaneously or after a significant interval had elapsed (14-30 years).
- Patients with locoregional disease underwent local excision and/or lymph node dissection; 1 patient received adjuvant radiotherapy.
- Patients with distant melanoma metastases received immunotherapy (PD-1 inhibition) and those with distant MCC metastases received chemotherapy.
- Simultaneous occurrence of both malignancies and the presence of comorbidities presented a management challenge; we treated the most aggressive malignancy the most aggressively, with consideration of the patients' comorbidities.
- Patients with concurrent MCC and melanoma present a management challenge.
- By aggressively treating the malignancy with the greatest effect on survival first, both diseases can be managed.
- Recent trials have shown that PD-1 inhibition is a promising option for patients with metastatic MCC, which could prevent conflicts in treatment strategies for patients with advanced MCC and melanoma in the future.

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Introduction

The incidence of skin cancer in white populations is increasing globally, likely caused by an increased exposure to sunlight, better detection, and an increasing life expectancy.[1,2] Most skin cancers consist of relatively indolent basal cell carcinoma or squamous cell carcinoma. Although generally not lethal, these cancers result in a health care burden through their sheer numbers and tendency to recur.

Much less common, but much more aggressive, are melanoma and Merkel cell carcinoma (MCC). Melanoma accounts for a minority of skin cancer cases but the vast majority of skin cancer deaths owing to its tendency to metastasize.[3] MCC is an equally aggressive, but exceedingly rare, neuroendocrine skin tumor with a propensity for locoregional recurrence and distant failure. Because of the similar clinical course of the 2 diseases, the rarity of MCC,

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and that clinicians are familiar with melanoma treatment, early-stage MCC is managed much the same as melanoma.[4]

Both cancer types share etiologies. Ultraviolet (UV) exposure is the greatest risk factor for melanoma and is believed to play a significant role in MCC development.[5] Second, the immune system plays a role in both diseases, with immunocompromised patients at an increased risk of MCC and melanoma.[4,6] Possibly because MCC shares risk factors with other malignancies, patients with MCC have an increased risk of other primary cancers. These consist mainly of melanoma and nonmelanoma skin cancer but also include hematologic malignancies and solid tumors.[7-10]

Localized and regionally metastatic melanoma and MCC are both managed with surgery, followed by adjuvant radiotherapy, when indicated. For distant metastatic disease, the options for both diseases have traditionally been limited. Chemotherapy for melanoma had only a marginal effect. Although chemotherapy for MCC has had a high response rate (similar to other small cell tumors), the response has been only short-lived.[11] Recently, however, immunotherapy with programmed cell death 1 (PD-1) checkpoint inhibition has shown impressive results with in both cancer types, changing the future of melanoma and, possibly MCC, treatment.[12-15]

In the present case series, we discuss several interesting cases of patients with both melanoma and MCC, discuss the treatment challenges, and highlight the role of PD-1 inhibition in disease management.

Case Report

The baseline characteristics of all 8 patients are listed in Table 1. We identified 6 male and 2 female patients. Their median age at diagnosis was 65 years for melanoma and 76 years for MCC. In 3 patients, melanoma and MCC were diagnosed simultaneously. In 4 patients, MCC was diagnosed 14 to 30 years after the initial melanoma diagnosis. Only in 1 patient was MCC diagnosed before melanoma (2 years). Of the 8 patients, 6 had an oncologic history, with 4 having a previous diagnosis of basal cell carcinoma. In the case of locoregional disease, the patients underwent local excision and/or lymph node dissection (LND). One patient received adjuvant radiotherapy. The 2 patients with distant melanoma metastases received immunotherapy (PD-1 inhibition) and the 2 with distant MCC metastases underwent chemotherapy. In most cases, the interval between the 2 diagnoses was significant, with, therefore, no conflicts between treatment strategies. In 3 patients, concurrent metastasized melanoma and MCC posed a management challenge. These cases have been described in more detail in the subsequent sections.

Patient 1

The first patient was man who was 80 years old at the diagnosis of MCC in 2014. His comorbidities included hypertension, angina, an abdominal aortic aneurysm, and a history of smoking. The oncologic history consisted of a melanoma of the right calf, excised in 1997, and radical cystoprostatectomy for urothelial bladder carcinoma. In late 2014, he had presented with an ulcerating axillary mass. Pathologic analysis showed axillary lymph node metastasis of small-cell neuroendocrine origin, with the immunohistochemical findings indicating MCC. No primary tumor could be found. In the interval between the diagnosis and axillary LND, he developed a palpable inguinal lymph node, which was biopsied during the axillary dissection. Axillary dissection yielded a metastatic lymph node conglomerate with a diameter of 5 cm with extracapsular extension, and another 19 negative lymph nodes. Inguinal lymph node biopsy revealed a melanoma metastasis, for which he underwent robot-assisted inguinal LND (0 of 7 positive lymph nodes). No additional metastatic lymph nodes were found. One year later in 2016, he had developed an inguinal melanoma recurrence, which was excised. An increase in S100B during subsequent follow-up examinations prompted positron emission tomography (PET)/computed tomography (CT) evaluation for staging, which showed melanoma metastases in the lung and spleen. Immunotherapy with PD-1 inhibition (pembrolizumab) was initiated, with therapy continuing at the last follow-up visit.

Patient 2

The second patient was a man, 61 years old at the MCC diagnosis, with a history of recurrent basal cell carcinoma. Early in 2015, he had presented with a lesion on the right forearm and regional axillary swelling, with both confirmed as MCC. A subsequent staging CT scan showed extensive retroperitoneal lymph node metastasis, confirming stage IV disease. In addition, the blood test results showed signs of chronic lymphocytic leukemia. Cisplatin and etoposide chemotherapy was initiated. The response evaluation after 3 months showed a response by the axillary metastases but progression of the retroperitoneal tumor mass, with compression and thrombosis of the inferior vena cava. Biopsy specimens of the retroperitoneal mass were taken because of the apparent discrepancy in response. The examination revealed melanoma metastases from an unknown primary tumor (*BRAF* and *NRAS* wild type). Immunotherapy was started with 2 courses of ipilimumab, followed by maintenance therapy with pembrolizumab. Shortly thereafter, he presented with neurologic symptoms, caused by hemorrhage from a cerebral metastasis that soon resolved. His disease was stable for approximately 1 year, until follow-up imaging showed progression of the axillary MCC metastases. It was decided to continue pembrolizumab treatment and resect the progressive lesion. Axillary dissection early 2017 yielded 54 lymph nodes, 2 containing metastases with a maximum size of 3.1 cm, without extracapsular extension. An additional finding was the presence of chronic lymphocytic leukemia in the axillary lymph nodes. Adjuvant radiotherapy was not administered, because the prognosis was likely to be determined primarily by the stage IV melanoma and the risk of regional nodal basin failure was deemed low. At the last follow-up visit, the patient was receiving maintenance therapy with pembrolizumab.

Patient 3

The third patient was a man aged 73 years at MCC diagnosis in 2015. His medical history included chronic obstructive pulmonary disease, diabetes, and hypertension with subsequently renal failure for which he had received a renal transplantation. In 2015, MCC and melanoma were diagnosed simultaneously. A lesion on the left buttock had been present for $>$ 1 year. Excision and pathologic examination confirmed a 6-cm MCC with an invasion depth of 8 mm and vascular invasion. A pT4b melanoma was excised from