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CASE REPORT

Combination of peptide receptor radionuclide therapy and immune checkpoint inhibitor in metastatic Merkel cell carcinoma

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ABSTRACT

A 78-year-old woman with metastatic Merkel cell carcinoma (mMCC) to the cervical and thoracoabdominal lymph nodes as well as cutaneous and subcutaneous lesions on the thighs and trunk was referred for peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-DOTA-TATE. Prior to PRRT, the disease had progressed through four cycles of pembrolizumab. Symptomatic benefit and a stable radiographic response was achieved following two cycles of [^{177}Lu]Lu-DOTA-TATE therapy (cumulative dose: 13.32 GBq) in combination with pembrolizumab. The patient could not receive further cycles due to complications from COVID-19 infection. PRRT in combination with immune checkpoint inhibitors is a promising therapeutic option for mMCC patients, refractory to conventional therapies.

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare malignant cutaneous cancer with poor outcome. As MCC express somatostatin receptors (SSTR), it makes them a good candidate for radioligand therapy with SSTR analogues. Also immune check point inhibitors (ICI) show promising results in treatment of metastatic MCC [1, 2]..

CASE PRESENTATION

A 78-year-old woman with a history of MCC of the left knee in 2019 underwent [^{18}F]FDG PET/CT for initial staging. The [^{18}F]FDG PET/CT did not show evidence of metastasis and the patient underwent surgery with wide local excision without sentinel lymph node biopsy. Radiation therapy to the primary site was planned for the patient but due to the COVID-19 pandemic, the patient did not return for treatment. After 18 months, following the development of unilateral lower extremity edema, she came back with a local recurrence in the left knee as well as multiple metastatic lymphadenopathies (LAP) in the cervical (Fig 1a), thoracic, abdominal, and pelvic regions. Some of the LAPs were bulky, such as a 10 cm pelvic mass (Fig 1b), which caused left lower limb edema (Fig 1c) and left side hydroureteronephrosis.

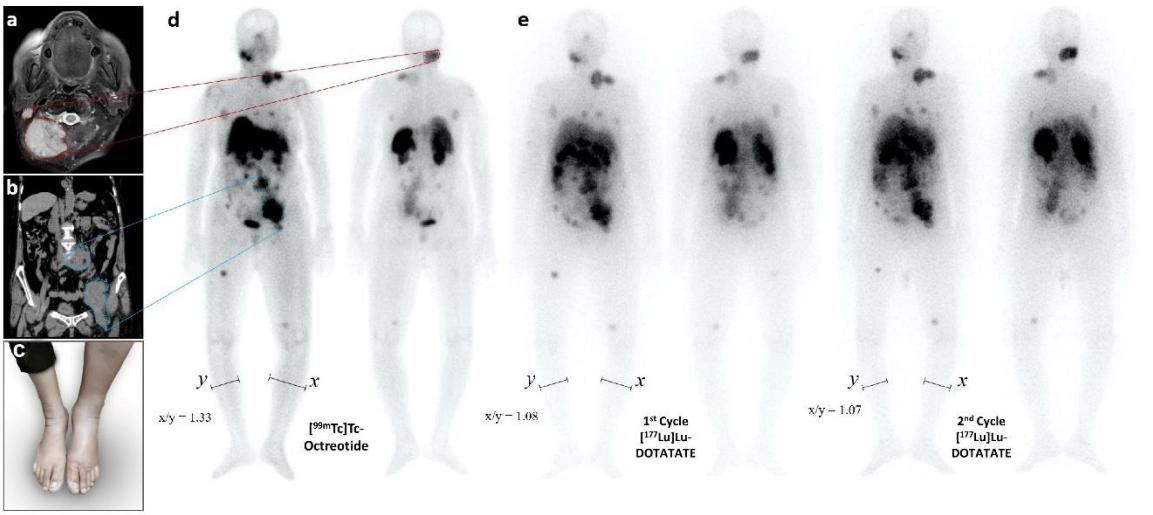

Figure 1. CT scan slices show multiple cervical (a) thoracic, abdominal and pelvic lymphadenopathies (b) which caused left lower limb edema (c). Numerous SSTR-avid metastatic lesions was detected using [^{99m}Tc]Tc-Octreotide scan (d). After two cycles of PRRT with [^{177}Lu]Lu-DOTA-TATE in combination with pembrolizumab, left lower limb edema was reduced however metastatic lesions remained stable with no significant change from the baseline scan (e)

The patient received four cycles of pembrolizumab but had progressive LAPs in several sites. Also, multiple tumoral deposits and subcutaneous soft-tissue lesions were noted in the abdominopelvic cavity and abdominal wall. Moreover, both thighs were involved by the tumor.

Due to disease progression, PRRT with somatostatin analogues was recommended in combination with ICI. To evaluate sufficient SSTR expression for PRRT with [^{177}Lu]Lu-DOTA-TATE, a [^{99m}Tc]Tc-HYNIC-TOC scan with single photon emission tomography/CT (SPECT/CT) was performed (Fig 1d). Fortunately, the patient had significant SSTR uptake in most lesions although some were not SSTR-avid in the abdominal cavity. Before PRRT, to estimate the function of the left hydronephrotic kidney, a Technetium-99m-L,L-ethylenedicysteine ([^{99m}Tc]Tc-EC) renal scintigraphy was performed and showed severely decreased function of the left kidney with 19% differential renal function. A double J nephrostomy was inserted to relieve the obstruction. Considering the rapidly progressive nature of the disease, the patient received two cycles of [^{177}Lu]Lu-DOTA-TATE separated by a 4-week interval and a cumulative activity of 13.32 GBq in combination with pembrolizumab. The PRRT was well tolerated with only minor hematologic adverse events (grade II anemia and grade I thrombocytopenia). The patient reported shrinkage of the bulky cervical and abdominal wall masses after the second cycle of PRRT concomitant with reduction of the left lower extremity edema, although post-treatment scans showed stable disease (Fig. 1e). The treatment with pembrolizumab was continued up to seventeen doses. The patient could not receive further cycles due to complications from COVID-19 infection. Six weeks after discontinuing pembrolizumab, she developed rapid tumor progression and significant deterioration of performance. Unfortunately, she passed away 32 months after the diagnosis, 21

months following metastasis confirmation and 6 months after initiation of PRRT.

DISCUSSION

Immunotherapy with PD-L1 inhibitors has changed the treatment landscape of mMCC. However, over half of mMCC patients will not have persistent benefit from these agents [3,4]. The majority of mMCC tumors have been shown to display SSTR uptake, making them good candidates for PRRT [5-7]. In Combination therapy with PRRT and ICIs for mMCC patients has reported in a few cases in the literature and has shown promising results with manageable adverse events [8-9]. We have recently conducted a comprehensive review on the role of PRRT in mMCC. Among 37 mMCC patients treated with PRRT alone or in combination with other therapies such as chemotherapy, radiation therapy and ICIs, the available data on treatment responses showed better outcomes with combination therapies in the mMCC patients [10]. When PRRT and ICIs are combined, priming doses of PRRT may act as a trigger for activation of immune response leading to permeation of T cells into the tumor microenvironment. This plausible mechanism of action has been recently shown to be useful in the prostate cancer landscape when ^{177}Lu-PSMA-617 was combined with pembrolizumab [11].

CONCLUSION

Metastatic MCC is an aggressive malignancy, however using novel treatment modalities like PRRT, SSTR analogues and immunotherapy using ICI show acceptable results which warrants further studies with larger population. New phase I/II clinical trials are evaluating the efficacy of combined PRRT and ICI in MCC patients (NCT04261855, NCT05583708).

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